# AUTOMATIC CONTROL STRATEGIES OF MEAN ARTERIAL PRESSURE AND CARDIAC OUTPUT

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# Automatic Control Strategies of Mean Arterial Pressure and Cardiac Output

MIMO controllers, PID, internal model control, adaptive model reference, and neural nets are developed to regulate mean arterial pressure and cardiac output using the drugs sodium Nitroprusside and dopamine

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# ABSTRACT

High blood pressure, also called hypertension is one of the most common worldwide diseases afflicting humans and is a major risk factor for stroke, myocardial infarction, vascular disease, and chronic kidney disease. If blood pressure is controlled and oscillations in the hemodynamic variables are reduced, patients experience fewer complications after surgery. In clinical practice, this is usually achieved using manual drug delivery. Given that different patients have different sensitivity and reaction time to drugs, determining manually the right drug infusion rates may be difficult. This is a problem where automatic drug delivery can provide a solution, especially if it is designed to adapt to variations in the patient's conditions.

This research work presents an investigation into the development of abnormal blood pressure (hypertension) controllers for postoperative patients. Control of the drugs infusion rates is used to simultaneously regulate the hemodynamic variables such as the Mean Arterial Pressure (MAP) and the Cardiac Output (CO) at the desired level. The implementation of optimal control system is very essential to improve the quality of patient care and also to reduce the workload of healthcare staff and costs. Many researchers have conducted studies earlier on modelling and/or control of abnormal blood pressure for postoperative patients. However, there are still many concerns about smooth transition of blood pressure without any side effect.

The blood pressure is classified in two categories: high blood pressure (Hypertension) and low blood pressure (Hypotension). The hypertension often occurred after cardiac surgery, and the hypotension occurred during cardiac surgery. To achieve the optimal control solution for these abnormal blood pressures, many methods are proposed, one of the common methods is infusing the drug related to blood pressure to maintain it at the desired level. There are several kinds of vasodilating drugs such as Sodium Nitroprusside (SNP), Dopamine (DPM), Nitro-glycerine (NTG), and so on, which can be used to treat postoperative patients, also used for hypertensive emergencies to keep the blood pressure at safety level.

A comparative performance of two types of algorithms has been presented in chapter four. These include the Internal Model Control (IMC), and Proportional-Integral-Derivative (PID) controller. The resulting controllers are implemented, tested and verified for three sensitivity patient response. SNP is used for all three patients' situation in order to reduce the pressure smoothly and maintain it at the desire level. A Genetic Algorithms (GAs) optimization technique has been implemented to optimise the controllers' parameters. A set of experiments are presented to demonstrate the merits and capabilities of the control algorithms. The simulation results in chapter four have demonstrated that the performance criteria are satisfied with the IMC, and PID controllers. On the other hand, the settling time for the PID control of all three patients' response is shorter than the settling time with IMC controller.

Using multiple interacting drugs to control both the MAP and CO of patients with different sensitivity to drugs is a challenging task. A Multivariable Model Reference Adaptive Control (MMRAC) algorithm is developed using a two-input, two-output patient model. Because of the difference in patient's sensitivity to the drug, and in order to cover the wide ranges of patients, Model Reference Adaptive Control (MRAC) has been implemented to obtain the optimal infusion rates of DPM and SNP. This is developed in chapters five and six.

Computer simulations were carried out to investigate the performance of this controller. The results show that the proposed adaptive scheme is robust with respect to disturbances and variations in model parameters, the simulation results have demonstrated that this algorithm cannot cover the wide range of patient's sensitivity to drugs, due to that shortcoming, a PID controller using a Neural Network that tunes the controller parameters was designed and implemented. The parameters of the PID controller were optimised offline using Matlab genetic algorithm. The proposed Neuro-PID controller has been tested and validated to demonstrate its merits and capabilities compared to the existing approaches to cover wide range of patients.

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2. Enbiya, S., Mahieddine, F. Muhammad Rafiq Mufti, "Multi-Drug Neuro-PID Adaptive Control of Mean Arterial Pressure and cardiac Output". Submitted to ISRN Biomedical Engineering Journal, 2013.

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| | |
|---|---|
| MAP | Mean Arterial Pressure |
| CO | Cardiac Output |
| SNP | Sodium Nitroprusside |
| DPM | Dopamine |
| NTG | Nitro-glycerine |
| IMC | Internal Model Control |
| PID | Proportional-Integral-Derivative |
| GAs | Genetic Algorithms |
| SROT | Simulink Response Optimisation Techniques |
| MMRAC | Multivariable Model Reference Adaptive Control |
| MRAC | Model Reference Adaptive Control |
| NNFT | Neural Network Fitting Tool |
| SISO | Single-Input Single-Output |
| MIMO | Multi-Input multi-Output |
| mmHg | Millimetres of Mercury unit |
| SVR | Systemic Vascular Resistance |
| HR | Heart Rate |
| SV | Stroke Volume |
| ICU | Intensive Care Unit |
| STR | Self-Tuning Regulator |
| MMAC | Multiple Model Adaptive Control |
| NNC | Neural Network Control |
| CAMAC | Control Advance Moving Average Controller |
| ANN | Artificial Neural Network |

| | |
|---|---|
| A/D | Analog to Digital |
| D/A | Digital to Analog |
| PI | Proportional-Integral |
| NE | Norepinephrine |
| SAC | Supervisory Adaptive Controller |
| CVP | Central Venous Pressure |
| DBT or DOB | Dobutamine |
| MPC | Model Predictive Control |
| RBO | Rule-Based Override |
| PNP or PHP | Phenylephrine |
| FDAM | Fuzzy Decision Analysis Module |
| HMM | Hemodynamic Management Module |
| TAM | Therapeutic Assessment Module |
| RLS | Recursive Least Squares |
| MPAP | Mean Pulmonary Arterial Pressure |
| DMRAC | Direct Model Reference Adaptive Controller |
| FDMM | Fuzzy Decision-Making Module |
| CI | Cardiac Index |
| SVRI | Systemic Vascular Resistance Index |
| PVRI | Pulmonary Vascular Resistance Index |
| FHCM | Fuzzy Hemodynamic Control Module |
| $MAPC_{NN}$ | Multiple Adaptive Predictive Control Based on Neural Networks |
| PD | Proportional-Derivative |
| FLC | Fuzzy Logic Controller |
| EDV | End Diastolic Volume |

| | |
|---|---|
| ESV | End Systolic Volume |
| RAP | Right Atrial Pressure |
| LAP | Left Atrial Pressure |
| DEX | Dextran |
| FM | Furosemide |
| $K_p$ | Proportional Gain |
| $K_i$ | Integral Gain |
| $K_d$ | Derivative Gain |
| G(s) | System Transfer Function |
| X(s) | Input System |
| Y(s) | Output System |
| FC | Fuzzy Control |
| IST | Integrating Self-Tuning |
| ARMA | Autoregressive Moving-Average |
| GFNN | Generalized Fuzzy Neural Network |
| RO | Response Optimisation |
| SDOT | Simulink Design Optimisation Technique |

# Chapter 1.

## INTRODUCTION

### 1.1 Background

Postoperative hypertension is a well-known complication of cardiac surgery patients and in 56-100% of cases of surgical coarctation repair. In fact, many studies have tried to find out the reasons of the increase in the blood pressure of the postoperative patients reported by Fox et al. in 1980 [1], and Rocchini et al. in 1976 [2]. Sodium Nitroprusside (SNP) is a powerful anti-hypertension drug. It quickly lowers the blood pressure in most postoperative patients and must be given intravenously with careful manipulation of the infusion rate to toxic side effects, reported by Tuzel in 1974 [3], Engeser et al. in 1982 and Ma in 2000 [4, 5]. The infusion of SNP and its effect on biological system poses a real problem in postoperative patients that has been reported by Treesatayapun in 2005 [6], Slate et al. in 1982 [7], Hahn et al. in 2002 [8] and Isaka et al. in 1993 [9]. The use of an automatic drug infusion control system in order to regulate the patients' blood pressure would reduce this complication in postoperative patients. In 1982, Slate and Sheppard developed a model for patients' response that showed there are large variations in the model parameters for different patients and their responses to the drug. This model has been used by many researchers to design several controllers such as the ones presented by Hahn et al. in 2002 [8] and Isaka et al. in 1993 [9].

In most post open heart surgery, patient suffers from hypertension which is caused by a severe vasoconstriction. An immediate use of vasodilator drugs is strongly recommended in order to reduce the risk of complications. Hemodynamic variables such as Mean Arterial Pressure (MAP) and Cardiac Output (CO) are commonly controlled using more than one drug. Several studies have investigated the automation of multiple drug-deliveries. Yu et al. in 1990 have developed a computer model to simulate the hemodynamic responses to Dopamine (DPM) and Sodium Nitroprusside (SNP) in a failing heart. They simulated the circulatory system with a nonlinear electrical analog model with baroreflex feedback [10]. Achuthan et al. in 1999 have used the computer model which was developed by Yu et al. in 1990 to test an indirect adaptive algorithm based on parameter identification and linear quadratic regulation [11]. Voss et al. in 1987 implemented an adaptive algorithm to control MAP and CO in anesthetized dogs with infusion of SNP and DPM [12]. Yu et al. in 1992 proposed an algorithm that utilized six model predictive controllers to regulate MAP and CO by administering positive inotropic and vasoactive drugs DPM and SNP respectively. They carried out tests on laboratory animals that were altered to exhibit symptoms of congestive heart failure [13]. Experiments on animal using multi-drug administration were also done by Koivo et al. in 1978 [14], Koivo in 1980 and 1981 [15, 16], Stern et al. in 1981 [17], and Kaufman et al. in 1984 [18].

Non-adaptive drug delivery systems proposed in the literature have serious limitations as they do not take into account the wide range of

patients' drug sensitivities. A number of authors have investigated control drug infusion systems based on adaptive neural networks and Fuzzy logic. These topics are reviewed later on in chapter 6.

## 1.2 Problem Definition

Automatic feedback control plays an important role in modem medicine. Research in feedback strategies to control physiological systems started in the early 1950s. Bickford [19] used electrical activity of patients' brain and the depth of anaesthesia index to actuate a feedback network which controls the dosage of anaesthetic administered to the patient. This is still an active research area, especially with regard to control of arterial blood pressure, as witnessed by the number of yearly publications. Many researchers have implemented automatic control system in order to maintain mean arterial pressure (MAP) and cardiac output (CO) by administering more than one drug. Most of the existing algorithms do not cover the wide range of patients' response to the drugs. The challenge therefore, is to design control schemes that would give a robust and optimum performance despite variations in the patients' responses to drugs. This research work will develop and investigate a number of approaches to solve this problem.

## 1.3 Research Contribution

The results of this research are expected to be helpful in understanding the contribution that computerized drug delivery systems can

make to improve patient care, especially hypertensive post-operative patients. Delivery of optimal drug infusion rates is important in order to maintain blood pressure and cardiac output at desired levels during and after surgical operation. This research has investigated a number of control approaches and developed a neural network control scheme that works with a range of patient's sensitivities to drugs. This scheme could be implemented in real time and tested in clinical trials.

## 1.4 Aims and Objectives

The aim of this thesis is to investigate, implement, test and compare both Single-Input Single-Output (SISO) and multi-loop feedback control strategies for regulating mean arterial blood pressure and cardiac output. The main objective of this research is to find the best solution to automatic drug delivery system. This is important as the uppermost concern of medical personnel is the quality of patients care.

To achieve the optimal solution for the complications that may occur in postoperative patients, the objectives of my research are:

- Investigate and design optimal control systems which could be suitable to implement in real time.
- Design appropriate controllers to satisfy postoperative patient's needs, such as the optimal drugs infusion rate, as required in several clinical situations in which it is necessary to infuse a drug in order to keep a patients' blood pressure at certain limits.

## 1.5 Thesis Structure

The rest of this thesis consists of six chapters. It is structured in a way that should make it easy to read. The outline of the structure can be summarized as follows:

*Chapter 2:* ***Literature Review:*** Presents the literature review of many researchers in relation to the problem of control of hemodynamic variables, such as MAP and CO.

*Chapter 3:* ***Control System and Tools:*** Introduces a brief overview of the control systems and some of the schemes which have been applied to the patient response model and algorithms which have been used to obtain optimal responses. This chapter covers the optimisation technique which is implemented to obtain the optimal values of controller gains.

*Chapter 4:* ***Control Schemes for*** **Single-Input Single-Output (SISO) Model*:*** Introduces the patient response SISO model and algorithms which have been used, presents the optimisation tools used to achieve the optimal performance of PID and IMC controllers. The simulation results and the comparison between the two controllers are presented.

*Chapter 5:* ***MRAC for Multi-Input Multi-Output (MIMO) Patient Response Model***: Presents the implementation and simulation results of the Model Reference Adaptive Control (MRAC) system to regulate patients' MAP and CO by computing infusion rates of SNP and DPM

*Chapter 6:* ***Adaptive Multi-drug Neuro-PID Control Scheme for Blood Pressure Control***: Presents the implementation and simulation results of the Neuro-PID control scheme, the procedure of

training the neural network, test and validation of the Neuro-PID controller.

*Chapter 7:* ***Conclusions and Future Work***: Presents the concluding remarks and recommendations for future work.

# Chapter 2.

## LITERATURE REVIEW

### 2.1 Blood Pressure

To understand how the various blood pressure lowering drugs work, one has to know about the complex ways in which blood pressure is controlled. There are two factors that influence blood pressure; cardiac output which is the quantity of blood being pumped by the heart, and peripheral resistance which is the resistance to flow. Resistance to flow is regulated by the size of the small arteries, which have muscle fibres in their walls, and can constrict and dilate. This means that when the blood pressure goes up it can do so in three ways, either by an increase in the cardiac output or by constriction of the arterioles, or by a combination of the two. In other words, blood pressure is the force applied against the walls of the arteries as the heart pumped blood through the body. So there are two ways of determining the pressure, by the force and quantity of blood pumped and the size and flexibility of the arteries.

Blood pressure is measured in millimetres of mercury unit (mmHg). It is classified into two types of blood pressure, high blood pressure (hypertension), when the blood pressure is constantly higher than the recommended level and low blood pressure (hypotension), when the blood

pressure is constantly lower than the recommended level. **Table** 2-1 presents the categories of blood pressure [20, 21].

**Table 2-1: Blood Pressure Categories.**

| CATEGORIES | SYSTOLIC | DIASTOLIC |
|---|---|---|
| Hypotension | ≤ 90 | ≤ 60 |
| Normal | 90 - 119 | 60 - 79 |
| Prehypertension | 120 – 139 | 80 – 89 |
| High Blood Pressure (Hypertension) | | |
| Stage 1 – Hypertension | 140 – 159 | 90 – 99 |
| Stage 2 – Hypertension | ≥160 | ≥100 |

## 2.2 Blood Pressure Medicines

Blood pressure medicines work in different ways to regulate the patients' blood pressure. Some eliminate extra fluid and salt from the body to lower the blood pressure; others reduce the heartbeat or relax and broaden the blood vessels. Often, two or more medicines work better than one. In this thesis we study and investigate two drugs related to the hemodynamic variables MAP and CO, namely Sodium Nitroprusside and Dopamine.

### 2.2.1 Sodium Nitroprusside (SNP)

SNP, brand name Nitropress is a potent rapid-acting vasodilator that works by relaxing the muscles in the blood vessels to help them dilate. Widening of arterial blood vessels decreases blood pressure. SNP is used for emergency treatment of hypertension, congestive heart failure, and to

keep blood pressure low during surgery. It is administered intravenously. SNP is a compound with the formula Na2[Fe(CN)5NO]·2H2O [22]. SNP breaks down in the blood and releases cyanide and nitric oxide. Nitric oxide enters the muscle cells in the walls of the blood vessels and causes them to relax. Cyanide is toxic in large quantities so SNP infusion rates must be kept brief or low, less than 2 μg/kg/min.

### 2.2.2 Dopamine (DPM)

DPM is an organic chemical in the catecholamine families, a class of compounds (drugs) that act by inotropic effect on heart muscle (causes more intense contractions) that, in turn, can raise blood pressure. At high doses, DPM may help correct low blood pressure due to low Systemic Vascular Resistance (SVR). It is available in only the generic form. It is used to treat hypotension, low cardiac output, and reduces perfusion of body organs due to shock, trauma, and sepsis. Also it increases Heart Rate (HR) and Stroke Volume (SV), leading to an increase in CO and MAP.

## 2.3 Blood Pressure Control Using a Single Drug

Since 1970s, several controllers have been developed to control the infusion rate of SNP in order to maintain the patients' MAP for hypertension patients. These controllers have been tested in computer simulations and animal experiments. There does not seem to be any published clinical trials

on automatic drug delivery systems. Some of the controllers have been tested clinically and achieved satisfactory results. Yu in 2006 has recommended that, incorporating a supervisory algorithm can be helpful to improve the reliability and safety of the controller. The control strategies that have been investigated in the literature are Proportional plus Integral plus Derivative (PID), Adaptive control which includes Self-Tuning Regulator (STR), Model Reference Adaptive Control (MRAC), Multiple Model Adaptive Control (MMAC), and Rule-Based Control (RBC) in addition to Neural Network Control (NNC). A summary of blood pressure algorithms can be found in [23] and is shown in **Table** 2-2.

Koivo, A.J in 1980, designed and employed the linear feedback controller to maintain the mean arterial blood pressure of dogs at desired level. The SNP were chosen as the antihypertensive drug to decrease the dogs' blood pressure and a syringe pump device received the control signal as input. The open loop system is made up of a syringe pump and the mathematical model of the dog. The closed loop system was operated in the range of 100 to 170 mmHg of blood pressure and the desired level of the blood pressure was 0 to 30 mmHg [15].

Automated drug delivery systems based on a feedback controller have been implemented to control patients' blood pressure. A computer-based closed-loop feedback control system has been employed in the University of Alabama Hospital Cardiac Surgical Intensive Care Unit for the

surveillance and treatment of 8500 patients following heart surgery [24] and [25]. In [14] a system has been implemented to control the blood pressure of rabbits in the range of 20 mmHg by infusion of the anti-hypertensive drug Trimethaphan Camsylate (Arfonad).

**Table 2-2: Summary of Blood Pressure Algorithms Reviewed [23].**

| ARTICLES | CONTROL SCHEME | CONTROLLER PERFORMANCE | | | CONTROLLER TEST | | |
|---|---|---|---|---|---|---|---|
| | | Settling Time (min) | Overshoot (mmHg) | Steady-state about the set-point (mmHg) | simulation | Animal Studies | Clinical Studies |
| Slate et al. [26] and [7] | Nonlinear PI | <10 | | ±10 | × | × | × |
| Arnsparger et al. [27] | STR | 2 | 30 | 10 | | × | |
| Mansour et al. [28] | STR | 5-20 | <10 | ±5 | × | | |
| Voss et al. [12] | CAMAC | 1.3-7.3 | 0-22 | -4 to 9.8 | × | × | |
| Kaufmann et al. [18] | MRAC (well-known time-constant and delay) | <5 | | ±5 | × | × | |
| Pajunen et al. [29] | MRAC (with time-varying parameters) | <5 | <15 | ±15 | × | | |
| Polycarpou et al. [30] | MRAC | 5 | | ±10 | × | | |
| He et al. [31] | MMAC | <8 | <5 | ±5 | × | × | |
| Martin et al. [32], [33] and [34] | MMAC | <10 | <10 | ±5 | × | × | × |
| Yu et al. [13] | MMAC | 3-10.5 | 0-12 | ±5 | × | × | |
| Rao et al. [35] and [36] | MMPC | 12 | | ±5 | × | × | |
| Isaka et al. [37] | Fuzzy Controller | <3 | <10 | ±5 | × | | |
| Ying et al. [38] | Fuzzy Controller | | | ±8 | × | | × |
| Chen et al. [39] | ANN | 5 to 20 | | ±15 | × | | |
| Kashihara et al. [40] | ANN | 2 | | ±5 | × | × | |

Where, STR is Self-Tuning Regulator, CAMAC is Control Advance Moving Average Controller, MRAC is Model Reference Adaptive Control, MMAC is Multiple Model Adaptive Control and ANN is Artificial Neural Network.

Acute postoperative hypertension is a well-known complication of cardiac surgery and untreated hypertension may cause the patient condition to worsen. The right way to make the postoperative patients safe is by implementing automatic control to maintain the blood pressure at a desired level through infusion of drugs such as SNP. Several researchers have presented a number of methods for automatic control of blood pressure which have been tested on animals and humans [25], [41], and [42]. In 2005 Zhu [43] proposed a novel adaptive Proportional-Integral (PI) controller for hypertension control. White noise was added to the system to reflect the real situation and the system was tested on different patients with different drug sensitivities and time delays.

SNP has a direct action on vascular smooth muscle which explains the rapid action within the first minute of infusion. In order to regulate the patients' blood pressure and keep it at a desired level, the infusion rate of drugs need to be continuous. Auer, L et al. in 1981 have employed a microprocessor to control the infusion rate necessary to drive the patients' blood pressure to the desired level within ±5% [44]. In addition, Koivo in 1981 implemented a microprocessor based controller to control the mean arterial blood pressure in dogs using SNP as a vasodilator drug, the drug delivery system contained a microprocessor (Motorola 6800), Analog to Digital (A/D) and Digital to Analog (D/A) converters. The signal output of the microprocessor was utilized to drive a syringe pump to inject an optimal drug

infusion rate into the body of the dog. The closed loop system has been tested on dogs and performed over the range of mean arterial pressure from 90 to 170 mmHg and over a period of time between 6 to 10 min. The proposed algorithm regulated the mean arterial blood pressure of dog within ± 10 mmHg from the desired level [16].

Automatic control system of arterial blood pressure by infusion of SNP has been used for patients who had elevated blood pressure after open-heart surgery at the Cardiac Surgical Intensive Care Unit at University of Alabama Hospital [24, 25]. A non-linear PID digital controller was tested on over 1700 patients. The investigations of the dynamics of the physiological response of patients to drug infusion are important for controller design. Also, the clinical experiences have shown that automatic control is safe and effective as compared to manual control [7].

The closed-loop feedback control is necessary to use for patients who have open-heart surgery to adjust the drug infusion rate depending on the state of arterial blood pressure. This is also used to maintain the patients' blood pressure near the desired level. Slate et al. in 1982 have reported that an adaptive multiple-mode multi-rate sampled data controller was designed using model based techniques, and implemented with a (LSI-11) microcomputer system [7].

Simulations and results of the nonlinear adaptive controller with experiments and clinical evaluations using a microcomputer implementation

show that system performance is improved as compared to the previous design. It is also noted that the system could be used in the operating room during and immediately after open-heart surgery [7].

A blood pressure control system has been developed based on the state predictive controller to reduce bleeding and avoid blood transfusion during open heart surgical operation using the drug Trimethaphan Camsilate. The dose response curves and the values of plant parameters have been used to derive a pure delay plus a first-order delay model. The accuracy and reliability of the system were evaluated by experimenting on dogs. The results have indicated the safety and stability of the system [45]. Before 1995, many controllers were applied to blood pressure control such as PID controllers, optimal controllers, adaptive controllers and rule based controllers. Most of the controllers did not include the dead time of the blood pressure response to drugs and also could not determine the drug infusion rate from the current blood pressure so researchers have suggested taking the dead time into account to improve the drugs' effects on the system stability and the transient response [41], and [9].

PI adaptive control has been implemented in [5] to maintained MAP at desired level using the vasoactive drug SNP with white or colored noise as disturbance. The adaptive controller can modify its behaviour in response to changes in the process dynamics and the character of the disturbances. During the simulation, the initial blood pressure was 150 mmHg and the

objective of the controller was to decrease blood pressure by 50 mmHg within ±15 mmHg. The system was disturbed by the noise. The patients' sensitivity to drug has effects on the system response, such as MAP and SNP infusion rate. The simulation results showed that the control system which has been implemented was able to regulate MAP within the suitable time [5].

An Internal Model Control (IMC) has been introduced in [46], and was defined for single input-single output, discrete-time systems. The basic structure of this IMC is shown in **Figure** 2.1. The controller has been implemented to maintain the patients' blood pressure at desired level using a single drug (SNP). The IMC system gain $K_1$ is the only parameter that may have an influence on system stability. The system gain was computed using an adaptation law described in [8]. In order to produce an optimal drug infusion rate, a genetic algorithms (GAs) optimization technique method based IMC has been developed and implemented. The IMC has been optimised using GAs optimization technique method as a tool of one of the Simulink Response Optimisation Techniques (SROT) method. The system has been tested on three types of patient, with different sensitivities to SNP in the presence of disturbances [47]. The GAs optimization technique method from simulink response optimisation toolbox was utilized to tune the system gain [48]. The simulation results of this system displayed good

performance and have achieved the optimal infusion rate for different kind of patients [8], [47], [26].

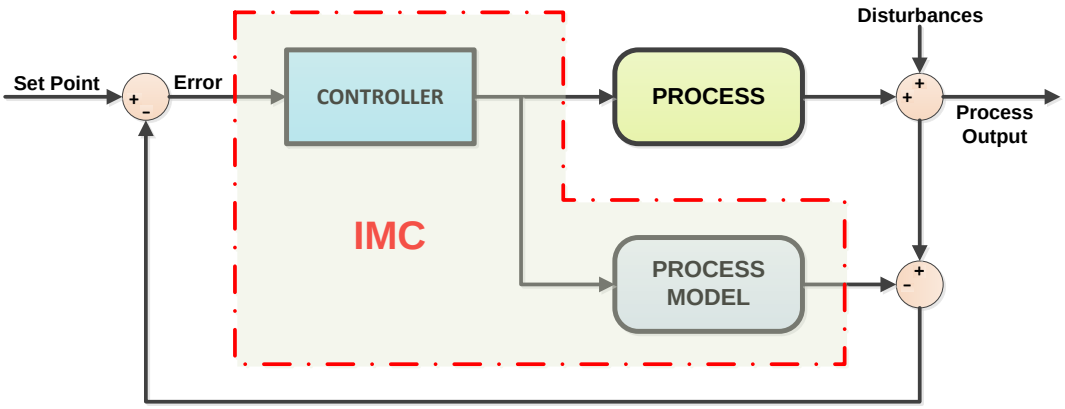



**Figure 2.1: Basic Structure of Internal Model Control (IMC).**

The comparative study of optimization algorithms for IMC based blood pressure control has been done [49]. Six methods of optimization techniques were compared to reveal the merits and capabilities of the algorithms. The study demonstrate that the traditional gradient descent method which has been utilized in [8] offered the weakest performance while the GAs optimization technique method achieved the shortest execution time to optimise the system parameters [49] and also has been utilized in the optimal IMC control of a pneumatic servo system [50].

Self-tuning control strategies, which synthesize directly or indirectly the controller parameters online have been used to deal with changes in the process characteristics. The self-tuning regulator was first introduced by Astorm and Wittenmark in 1973 [51]. In [17] a self-tuning regulator was

implemented to automate blood pressure control. The self-tuning regulator is designed to maintain reliable performance under a variety of conditions.

A non-adaptive controller has been used to automate blood pressure regulation and from several researchers this algorithm has proven the safety of closed-loop control for high blood pressure. But in order to control hemodynamic variables such as MAP and cover the wide range of patient characteristics, adaptive control has been implemented with parallel least-squares estimation routines to regulate MAP using a single drug SNP [52]. Behbehani et al. in 1990 presented an adaptive control scheme and reported that this algorithm is suitable for regulating the MAP using SNP [53].

Stochastic adaptive control is the control of a partially known or completely unknown stochastic system. A physical system is often subject to perturbations and a model for a physical system is only an approximation so there are unmodeled dynamics. These perturbations or unmodeled dynamics are often described by noise entering the model. For physical systems, it is often important or even necessary to control the system to have some desirable behaviour.

As a result of the need for automated drug infusion control, many studies have been made to develop an automatic control system to maintain blood pressure within physiological limits. Stochastic adaptive controllers have been developed and applied to control dogs' blood pressure. Two drugs have been used, one is Levophed$^{TM}$ named as Norepinephrine (NE)

was infused to elevate the blood pressure and the other is SNP to reduce the blood pressure [27].

In [28] the comparison between two algorithms indicated that the one-step-ahead minimum adaptive controller has the better performance of producing a smoother control action with less oscillation in the infusion rate than minimum variance adaptive controller. The important advantage of their controller, is that it can adjust the systems' parameter online depending on the changes in the circulatory state within eight steps as presented in the cycle of program control loop as shown in **Figure** 2.2, see [28].

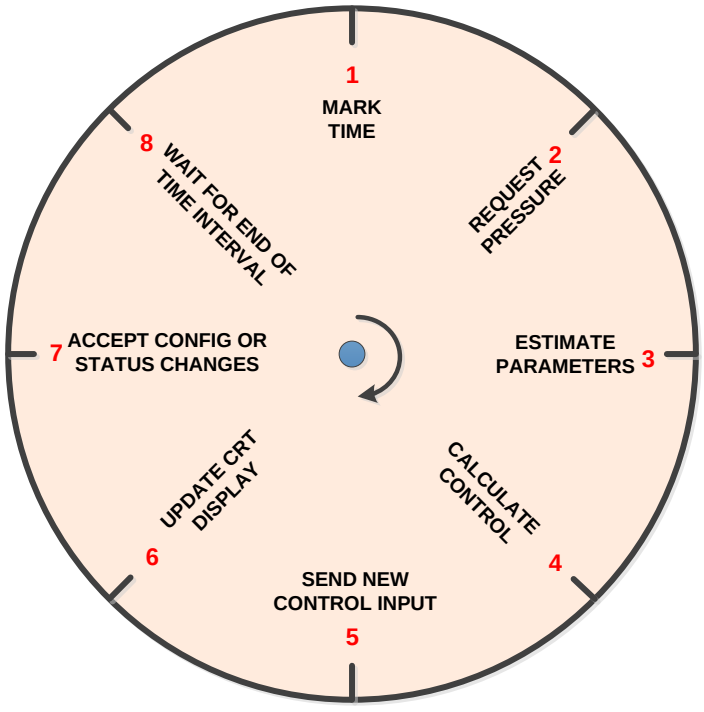



**Figure 2.2: Graph of Program Control Loop.**

Many researchers have tried to demonstrate the performance of Model Reference Adaptive Control (MRAC) for regulates of hemodynamic variables. This controller has been implemented to regulate the infusion rate of SNP in order to regulate blood pressure [18].

The Multiple Model Adaptive Control (MMAC) has been implemented and tested on animal (dogs). In the treatment of hypertension, infusion of SNP was automated using MMAC in order to regulate the patients' blood pressure. The following performance criteria, which have been introduced by Slate in [26], were used to evaluate the controller in [31]:

- Undershoot not more than 10 mmHg.
- Settling time from 5 to 10 mines.
- Steady-state error within ±5 mmHg.

In addition, other researchers have proposed MMAC to regulate the blood pressure. Martin et al. in 1987 have presented this algorithm with pole-placement, via state-variable feedback to control blood pressure using SNP; also they have employed Proportional-Integral (PI) control to obtain zero steady-state error. The authors reported that a wide range of patient characteristics were controlled including noise which is used to model the variance of sudden changes in patients' blood pressure up to 4 mmHg [32].

An adaptive controller needs supervisory functions in order to function well in changeable system environment such as during cardiac surgery. The

supervisory functions guarantee that adaptation only is performed when proper excitation is available. Due to the complexity of arterial pressure control during cardiac operation, in 1992, Martin et al. have developed and implemented a Supervisory Adaptive Controller (SAC) in closed-loop control in order to regulate MAP using SNP. This controller includes a pole-placement and proportional-plus-integral regulator, which has been used to deal with aggressive step response characteristics. The multiple-model adaptation was employed to guarantee fast and stable adjustments for any changes in patient parameters, and the supervisor was used to provide safety and efficiency of control in the presence of disturbances during cardiac operation [34].

Fuzzy control based on the general-purpose fuzzy logic production system has been implemented to regulate patients' MAP by controlling the infusion rate of antihypertensive drugs such as SNP. In most studies, the patients' model has been described by a first-order linear model with two time delay, one time-delay represents the initial transport delay and the other represents the recirculation time delay. This patient model has been used with different patients' sensitivities to SNP [7, 26, 54]. In 1990 Ying and Sheppard [55] presented and implemented a fuzzy controller to regulate MAP of pigs by infusion of SNP. The fuzzy controller was designed by using experts' knowledge and experience without any mathematical models involved.

Many researchers have focused on the complication problems of postoperative hypertension in cardiac patients; the automatic drug delivery control system is desirable to achieve optimal drug infusion rate. Feng et al. in 2006 have designed and implemented control system using adaptive PI and Fuzzy controllers in order to reduce harmful oscillations in MAP and control the infusion rate of SNP depending on the patients' conditions [56].

## 2.4 Blood Pressure Control Using Multi Drugs

Research into control of hemodynamic variables such as blood pressure was started by Slate et al. in 1979 using a PID controller in order to lower MAP by infusing SNP [57]. Since then, more complex control algorithms have been used in order to automate regulation of hemodynamic variables. In 1993 Isaka and Sebald presented an extensive review of SISO systems, and they drew attention to more important issues of safety and robustness when dealing with multiple drugs to control more than one hemodynamic variable [9].

Adaptive control has been used by Martin et al. [34] and Kwok et al. [58] in order to regulate blood pressure during surgery. In addition many research efforts have been made to regulate MAP and cardiac output (CO). Serna et al. in 1983 reported on the simultaneous control of CO and MAP using DPM, a drug used to increase MAP and CO on the other hand SNP was used to increase CO and decrease MAP. They designed a computer

based controller which combines adaptive control schemes and supervisory functions. Their simulations and animal experiments have indicated that pole-placement self-tuning controllers are potentially useful in adjusting the infusion of sodium nitroprusside when infused as a single drug or when combined with another drug such as dopamine [59].

Lau et al. in 1984 have presented a comparison of the utilization of different types of adaptive controllers which have been used to adjust the infusion rate of two drugs, DPM and SNP, in order to control SVR and CO. The controller's robustness was tested during simulation using three values of the system sensitivity parameters. These values represented the patients' sensitivity to drugs [60].

In clinical practice, the control of patients' blood pressure is commonly treated by multiple drug infusions. An adaptive control algorithm has been implemented by McInnis and Deng in 1985 to control MAP and Central Venous Pressure (CVP) using both an inotropic agent and a vasoactive agent. An inotropic drug was utilized to increase the CO, MAP and CVP, and a vasodilator drug to decrease the afterload. Their simulation results have demonstrated CO increased by 25% [61].

In 1986 the simultaneous control of MAP and CO in anesthetized dogs was presented by Voss et al. [62]. The moving average controller and a modification of the minimum variance self-tuning controller was used to regulate the infusion of both vasodilator drug SNP, and a positive inotropic

agent, Dobutamine (DBT). Their simulation results have demonstrated the performance of the system. MAP was decreased to within 5 mmHg of the desired level with range of overshoot from zero to 22 mmHg, and CO was increased to within 0.05 l/min of the desired level in 11.8 minutes with range of overshoot from zero to 0.18 l/min. Also CO could not reach the desired level as set-point for 32 minutes with maximum infusion rate of DBT, on the other hand MAP was maintained at the desired set-point level with range of average error from -4 to -9.8 mmHg after 10 minutes of the transient control period, and CO reached the value of desired level after 10 minutes with range of average error from -0.026 to -0.05 l/min [62]. Voss et al. research in 1987 demonstrated the implementation of a multivariable drug delivery system was able to achieve the optimal performance but was not able to show adequate evidence for clinical applications [12]. Their simulation results are presented in the **Table** 2-2.

Barney and Kaufman in 1990 presented the MRAC implementation to concurrently control MAP and CO by infusing two drugs, DPM and SNP. The adaptation weights for “a two-input two-output” Multi-Input Multi-Output (MIMO) system was developed and utilized to update the parameters. The controller was tuned using 6×6 time invariant weighting matrices. The controller was first tuned using a single-input single-output system and then was tuned using a two-input two-output system. The weights which were represented as matrices T and $\overline{T}$ were computed for one-input one-output

system with time delays and drug infusion limits and then for two-inputs two-outputs [63].

In 1990, Yu et al. developed a computer model to approximate the hemodynamic responses of inotropic drug such as DPM and vasodilator drug such as SNP in the case of acute left ventricular pump failure. This model was proposed to support the design of a multiple drug delivery infusion system. A non-linear electrical analog circuit has been utilized with baroreflex feedback to simulate the circulatory system. The model was programmed by PASCAL and implemented on an IBM AT microcomputer. This model needs more development to compute the hemodynamic online because of the large number of equations required to be solved per heartbeat. DPM was used to reduce renal vascular resistances at low infusion rate. With this model the response to DPM cannot be simulated because the systemic resistances have been lumped into a single element [10].

In order to regulate MAP and CO in congestive heart failure by updating the infusion rates of SNP and DPM, Yu et al. in 1992 have designed and employed multiple-model adaptive predictive control. The 36 linear small-signal models have been implemented to span the entire space of anticipated responses. The model is reduced to six models with the highest probabilities used in the control calculations to reduce computation time. The algorithm was based on MMAC and utilized model predictive controllers to provide reliable control in each model. The controller has been

tested and evaluated on laboratory animals. The simulation results have demonstrated the controller performance with 3 to 10.5 minutes of settling time and 0 to 12mmHg overshoot, and within ±5 mmHg of steady-state [13].

In 1998, Palerm et al. presented the implementation of a multivariable, indirect-adaptive pole placement controller to regulate MAP and CO by adjusting the infusion rates of SNP and DPM. The control objective was to drop MAP by 20 mmHg from the value of 119 mmHg and to drop CO by 5 ml/min/kg from the value of 131 ml/kg/min. The system still needs more development to cover more possible system variations [64].

Linkens and Nie in 1992 presented control systems and fuzzy decision-making in order to deal with the problem of multivariable control of hemodynamic variables such as MAP and CO. The application of the proposed algorithms was to regulate simultaneously both CO and MAP by infusing the vasoactive drug SNP and an inotropic drug DPM [65].

The congestive heart failure is one of the heart problems and in this case Gopinath et al. in 1995 presented a multirate Model Predictive Control (MPC) design for regulating MAP and CO by controlling the infusion rate of SNP and DPM. A selective linearization technique was introduced to reduce computation time. The novel Rule-Based Override (RBO) to the MPC controller was implemented to avoid extremely slow responses of the initial DPM infusion [66].

In 1998, and 2000 Huang et al. presented the development and validation of a fuzzy-logic-based automated drug delivery system using a nonlinear canine circulatory model. This system was implemented for managing the hemodynamic status of animal using four drugs, DPM, phenylephrine (PNP), SNP and NTG. The algorithm was composed of three parts, Fuzzy Decision Analysis Module (FDAM) which was utilized to appraised the status of the patient and to choose a suitable therapeutic strategy after the evaluation, a Hemodynamic Management Module (HMM) which was employed to determine the correct drug dosage based on the current states of the patient, and a Therapeutic Assessment Module (TAM) used to schedule drug delivery by evaluating several parameters, and considers each case individually as recommended by the FDAM [67, 68].

The indirect adaptive control scheme based on recursive identification and linear quadratic regulation has been implemented in 1999 by Achuthan et al. on a nonlinear canine model to control the infusion rates of DPM, SNP and NTG in order to maintain MAP and CO. The recursive identification was conventional Recursive Least Squares (RLS) and a modified version (MRLS) to follow large parameter changes [11].

The complication problem in heart disease has different categories such as congestive heart failure, post-operative hypertension, and sepsis shock. From this point, in 1999 Rao et al. have presented a model predictive controller and tested it on a nonlinear canine circulatory model to regulate

the hemodynamic variables considering the critical care conditions. The controller has been tuned on a linear plant model and tested on a nonlinear model. This algorithm has been employed to regulate MAP, Mean Pulmonary Arterial Pressure (MPAP) and CO using SNP for arterial vasodilation and DPM to enhance cardiac performance. PNP was used as an arterial vasoconstrictor and NTG is a venodilator. Their simulation results have demonstrated a settling time of 10 minutes for MAP and MPAP and from 15 to 20 minutes for CO [69].

In 1999, Rao et al. employed a multiple model predictive controller to regulate MAP and CO of a mongrel dog by controlling the infusion rate of SNP, DPM and PNP. The simulations were conducted in order to regulate the outputs within a range of values [70].

Design of robust control is a challenging task because of complications such as nonlinear systems' behaviour, significant changes in dynamics from patient to patient, and variations in the patients' response to drugs. Ozcelik and Palerm research focused on this problem [71]. They developed a Direct Model Reference Adaptive Controller (DMRAC) to deal with uncertainty in time delays and the parameters of the patients' model using a two-input two-output first order system with delays which was developed by Yu et al. in 1992. The controller they developed was based on a simple adaptive control scheme of MIMO plants first proposed by Sobel et al. in 1979 [13, 71-73] respectively.

Fuzzy logic control has been implemented by Huang et al. In 1998, and 2000 [67, 68] to manage the parameters of hemodynamic states using multiple drugs. The controller has been designed using three components:

- A Fuzzy Decision-Making Module (FDMM) used to recommend a therapeutic strategy for the patients' case based on the Cardiac Index (CI), the Systemic Vascular Resistance Index (SVRI), and the Pulmonary Vascular Resistance Index (PVRI).
- A Fuzzy Hemodynamic Control Module (FHCM). From the current patients' states of MAP, MPAP, and CO, this module is used to change the drugs dosage depending on the current states of the patient.
- TAM is employed to schedule drug delivery based on the patients' case from the FDMM and the drug changes which has been determined by the FHCM.

In 2003, a Fuzzy-logic based automatic control system was implemented by Bauernschmitt et al. to observe and handle any changes in hemodynamic variables such as MAP, CO, CVP and SVR using the drugs noradrenaline, dopamine and nitrates. The hemodynamic parameters and the drugs were linked by knowledge-based rules in a fuzzy-logic system [74].

In recent years, there was active research into automated control systems for regulation of MAP and CO using multi drugs. In 2003, Rao, Aufderheide, and Bequette presented experimental studies on multiple model predictive control system for regulating MAP and CO using SNP and

DPM for canines under the influence of two different anesthetics, isoflurane and halothane. They also presented the comparison with manual control of MAP and CO [36].

In 2006 Kashihara presented the implementation of a Multiple Adaptive Predictive Control Based on Neural Networks ($MAPC_{NN}$) to regulate the nonlinear responses of hemodynamic variables MAP and CO in acute heart failure using an inotropic agent such as DBT and a vasodilator agent such as SNP. The algorithm has been designed and evaluated in actual heart failure of a dog under unexpected changes of the patients' sensitivities to drugs [75].

The regulation of hemodynamic variables such as MAP and CO is extremely desirable during operation and in post cardiac operation. Kumar et al. in 2009 presented a fuzzy Proportional-Derivative (PD) controller to regulate MAP and CO by infusing three drugs DPM, SNP and phenylephrine (PHP). **Figure** 2.3 displays the block diagram of the Fuzzy Control (FC) system, with 25 rules as shown in **Table** 2-3. The relationship between CO and HR is explained by **Equation** (2.1) and **Equation** (2.2). The problem which faced Kumar et al. is the mathematical models for different drug actions. To improve the performance of the proposed controller, they modified the controller as "self-organized Fuzzy Logic Controller (FLC)" or as a neuro fuzzy controller [76].

$$\mathrm{CO} = \mathrm{SV} \times \mathrm{HR} \tag{2.1}$$

where, CO is the cardiac output.

SV is the stroke volume.

HR is a heart rate.

$$\mathrm{SV} = \mathrm{EDV} - \mathrm{ESV} \tag{2.2}$$

where, EDV is the End Diastolic Volume.

ESV is the End Systolic Volume.

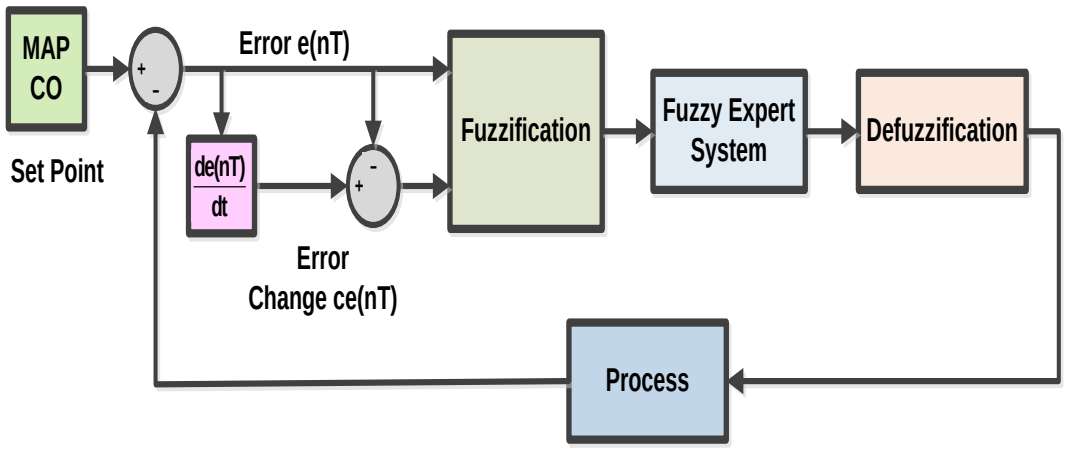



**Figure 2.3: Block Diagram of Fuzzy Control System.**

**Table 2-3: Rule Based for The Fuzzy Controller [76].**

| ce(nT) / e(nT) | NB | NM | NS | Z | PS | PM | PB |
|---|---|---|---|---|---|---|---|
| **NB** | - | - | - | - | - | - | - |
| **NM** | - | - | - | - | - | - | - |
| **NS** | - | - | NB | NB | - | - | - |
| **NO** | - | - | NO | NO | Z | - | - |
| **PO** | - | - | PS | PS | Z | Z | NO |
| **PS** | - | - | PS | PS | PS | PO | Z |
| **PM** | - | - | PB | PM | PM | PS | PB |
| **PB** | - | - | PB | PS | PB | PM | PB |

Where, **e(nT)** represent the error and **ce(nT)** represent the change of error, and the terms which have been considered are:

| | | | |
|---|---|---|---|
| NB | : Negative Big. | NM | : Negative Medium. |
| NS | : Negative Small. | Z | : Zero. |
| NO | : Negative Zero. | PO | : Positive Zero. |
| PS | : Positive Small. | PM | : Positive Medium. |
| PB | : Positive Big. | | |

In 2009, Sugimachi et al. presented the controlling of multiple hemodynamic variables such as CO, Right Atrial Pressure (RAP) and Left Atrial Pressure (LAP) with multiple cardiovascular drugs such as Dobutamine (DOB), SNP, Dextran (DEX) and Furosemide (FM) [77]. Their studies have shown direct control of hemodynamic variables is unfeasible even with different control engineering methods. The problem is complicated due to anomalies of cardiovascular properties, including pump function, vascular resistance, and blood volume. They used the extended version of Guyton's circulatory equilibrium framework to identify these properties. This version has also been presented in 2004 and 2005 by Uemura et al., [78, 79], Figure 2.4 **Figure** 2.4 shows the extended version of Guyton's model see [77].

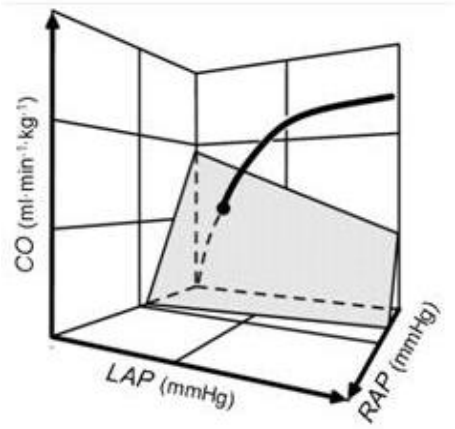



**Figure 2.4: Extended Version of Guyton's Model [77].**

## 2.5 Summary

This chapter has covered most of the control algorithms that have been implemented by many researchers to regulate the hemodynamic variables using single and multiple drugs. As this literature survey revealed, control of MAP and CO is an active research area and a challenging task.

In next the chapters design, development, implementation and simulations results of a number of SISO and MIMO control strategies will be presented using the drugs SNP and DPM to regulate MAP and CO.

# Chapter 3.

## CONTROL SYSTEM AND TOOLS

### 3.1 Introduction

In general a feedback control system consists of subsystems and processes (or plants) assembled for the purpose of obtaining a desired output with desired performance, given a specified input. Control has become essential for design of experimental apparatus and instrumentation which is usually used in sciences and it will be more important in the future. The principles of control have an impact on different fields such as economics, biology, and medicine. [80].

A control system is an interconnection of some components utilized to maintain the optimal or desired result. The assortment of components could be a part of a control system as electrical, electronic, mechanical, human, or any grouping of these. The optimal result of the control system is a value of the variable in the system, for example, the speed of DC or AC motor in plant, the temperature of the heating system in the house, the level of liquid in a tank, or the blood pressure in patients' circulatory system. The output of the control system is called the controlled or manipulated variable [81]. The component or process which needs to be controlled can be represented by a block as shown in **Figure** 3.1.


**Figure 3.1: General BLock Diagram of a Process in input/output Form.**

To maintain a physical quantity, such as pressure, flow or temperature at a desired level during a technical process, this quantity can be controlled either by means of open loop control or closed loop control. The control systems are generally classified as either open loop control system or close loop control system.

- Open loop control system (without feedback).
- Closed loop control system (with feedback).

### 3.1.1 Open Loop Control system

An open loop is not self adjusting, it is controlled by its input only, and its input and output are unrelated. Open loop control has no feedback and therefore is incapable of making automatic adjustments. This is the reason an open loop control system is not suitable for use as a complex control system. An open loop control system utilizes a controller or control actuator to obtain the desired system response without feedback. **Figure** 3.2 shows the general structure of open loop control system [82].

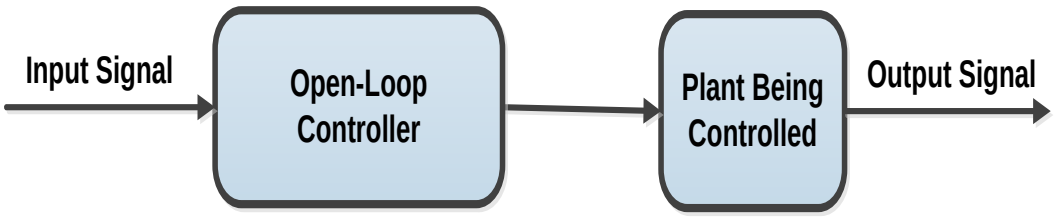



**Figure 3.2: General Structure of Open Loop Control.**

### 3.1.2 Closed Loop Control System

In a closed loop control system there is some items between the input signals (reference, or set point) and controlled the output signals. And there is one item such as a measurement or sensor device which uses the output signal as feedback to make the comparison and produces the error signal to be the input of the controller. A feedback control system often uses a function to maintain a relationship between the system input, called reference input and system output or feedback signal to control the process. The differences between input signal and output signal through feedback is the error signal. The general structure of a closed loop control system is shown in **Figure** 3.3 [82].

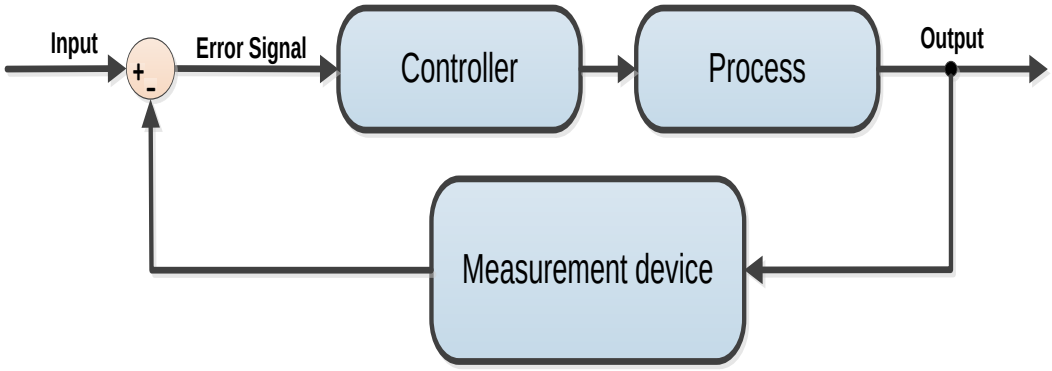



**Figure 3.3: General Structure of Close Loop Control System.**

## 3.2 Control Algorithms

The objective of a controller design is to ensure that the resulting system is stable, achieves its performance objectives, and is robust to disturbances such as changes in workloads. These objectives are achieved by properly designing feedback loops. Controller design is a three-step process:

- System modelling, i.e. the definition of a model.
- System analysis, i.e. the study of the model behaviour.
- Controller design. The design technique is the algorithm or methodology used within the control algorithm in order to generate the control action variables from the measured variables.

### 3.2.1 PID Control

PID control also referred to as three-term control is widely used in many fields such as process industries, economics, biology, and medicine because of its simple structure and robustness to modelling errors. It has a long-term record of giving satisfactory performance. In process control, PID control is applied in more than 95% of the control loops [83]. In the past decades there are many researchers dealing with the method of PID controllers tuning for different processes. The general PID control law is given by **Equation** (3.1):

$$u(t) = K_p e(t) + K_i \int_0^t e(t)dt + K_d \frac{de(t)}{dt} \quad (3.1)$$

where:

u(t) : Control signal.

$K_p$ : Proportional gain, a tuning parameter.

$K_i$ : Integral gain, a tuning parameter.

$K_d$ : Derivative gain, a tuning parameter.

e : Error between setpoint and process output.

In conventional PID control, once well-tuned gains are obtained, the controller usually exhibits good performance. However, when the dynamic characteristics of the system are time dependent or the operating conditions of the system vary, it is necessary to retune the PID and PI parameters again. The manual tuning of controllers, which requires optimization of the parameters, is a time-consuming task. To deal with this difficulty, much effort has been invested in developing systematic tuning methods. Many of these methods depend on knowledge of the plant model. Some of these tuning methods have been described by Astrom et al. in 1993 [84].

In this thesis the genetic algorithms (GAs) optimization technique method is used to obtain optimal values for the PID gains.

The parameters of the PID controller can be adjusted by experiment, trial and error or by using one of the many tuning techniques. **Table** 3-1 shows how the PID gains affect system response, stability and steady-state

error. In the conventional PID control algorithm, the proportional (P), integral (I) and derivative (D) terms are placed in the forward loop. These PID controllers are suitable for controlling stable processes with small time delays.

**Table 3-1: The Rules for Tuning PID Controller Parameters.**

| Parameter | Speed Of Response | Stability | Accuracy |
|---|---|---|---|
| If $K_p$ increases | increases | Deteriorates | Improves |
| If $K_i$ increases | Decreases | Deteriorates | Improves |
| If $K_d$ increases | increases | Improves | No impact |

### 3.2.1.1 Open-Loop and Closed-Loop Control Example

The characteristics of a PID controller are presented in **Table** 3-2 and explained with some examples. **Equation** (3.2) describes a second order transfer function model of a plant, and the open-loop and close-loop Simulink control diagrams without a controller are shown in **Figure** 3.4, and **Figure** 3.5. The outputs of the two systems are depicted in **Figure** 3.6. The plant output signal cannot reach the desired amplitude of (1) without the use of a controller.

Plant transfer function:-

$$\mathrm{u(t)} = \frac{\mathrm{Y(s)}}{\mathrm{X(s)}} = \frac{1}{s^2 + 10s + 20} \tag{3.2}$$

Where, X(s) is the input of the system and Y(s) is the output of the system.

**Table 3-2: The Characteristics of a PID Controller.**

| Parameter | Rise Time | Overshoot | Settling Time | Steady-State Error |
|---|---|---|---|---|
| If $K_p$ increases | Decreases | increases | Small Change | Decreases |
| If $K_i$ increases | Decreases | increases | Increase | Eliminates |
| If $K_d$ increases | Small Change | Decreases | Decreases | Small Change |

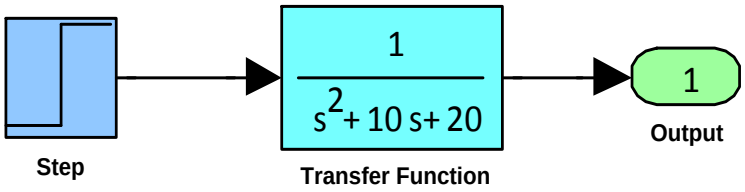



**Figure 3.4: Simulink Model of Open-Loop Control System.**

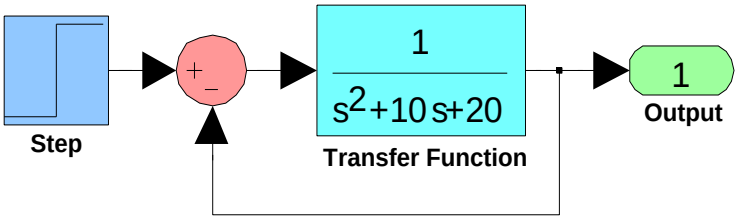



**Figure 3.5: Simulink Model of Closed-Loop Control System.**

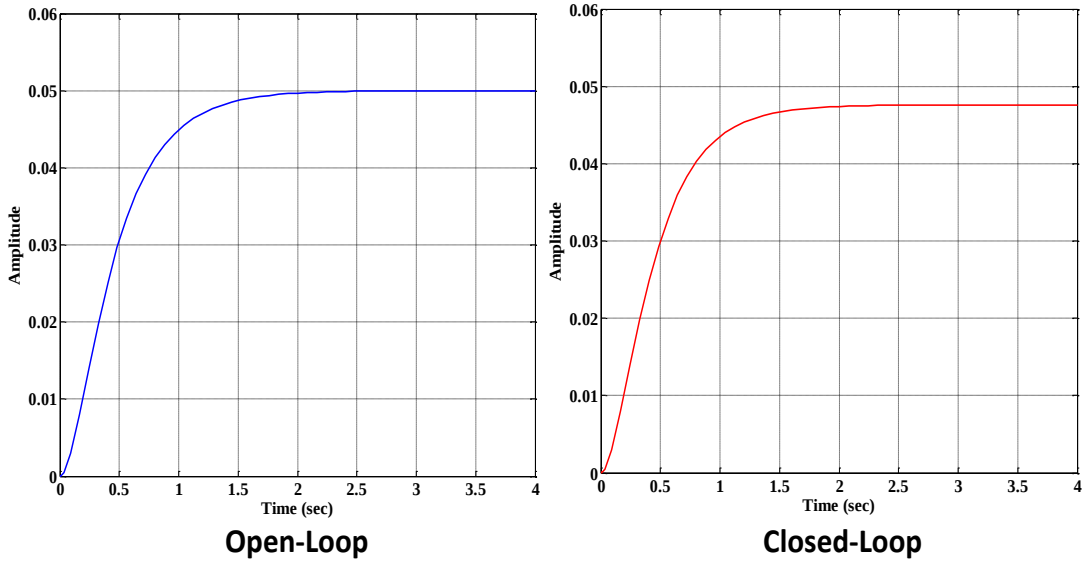



**Figure 3.6: Open-Loop and Close-Loop Control System Response without Controller.**

#### 3.2.1.2 The Objectives of Designing a PID Controller

In general we have to obtain an open-loop system response and from that we can determine what needs to be improved. The parameters of the controller can be adjusted to achieve the optimal system response as shown in **Tables** 3-1 and 3-2. Increasing the proportional gain will improve the rise time. The overshoot and settling time can be improved by increasing the derivative gain. Using an integral term will eliminate the steady-state error. However, system stability may suffer so careful tuning of the integral gain is required. When dealing with systems with transport delay, derivative action does not give good performance so it is better to use PI terms only. Derivative action amplifies noise in the output so filtering should be applied before using it.

#### 3.2.1.3 Proportional Control – Example

The proportional gain ($K_p$) reduces the rise time, increases the overshoot, does not affect settling time much, and decreases the steady-state error but does not remove it entirely. In this simulation example we used a proportional controller (P). **Figure** 3.7 shows the Simulink diagram of the system with proportional control. The system responses with different value of $K_p$, 100, 200 and 300, are depicted in **Figure** 3.8.

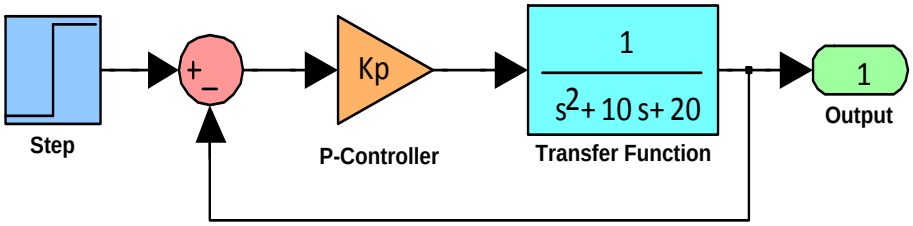



**Figure 3.7: Simulink Block Diagram of Control System with P Controller.**

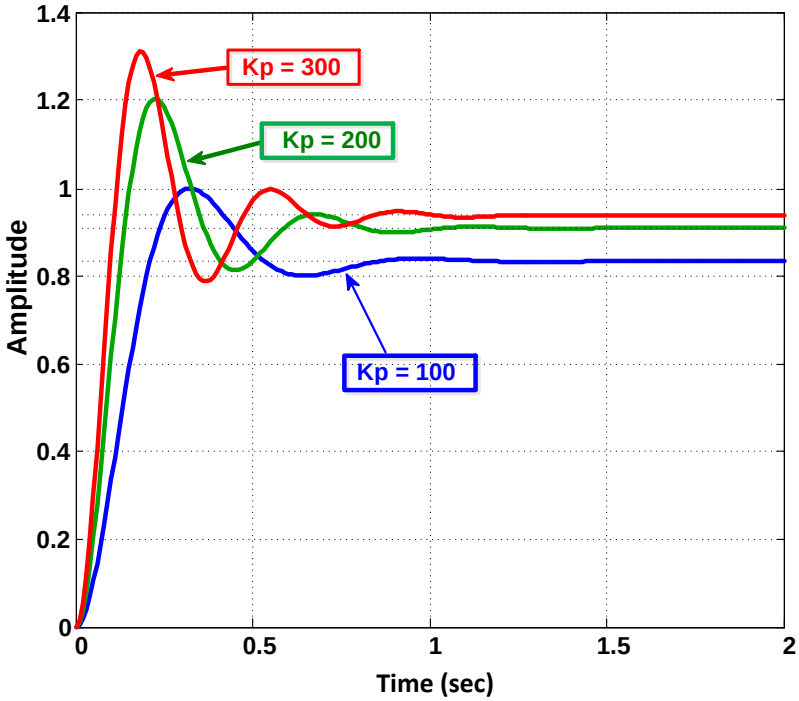



**Figure 3.8: System Responses Using P Controller.**

### 3.2.1.4 Proportional - Derivative Control – Example

The derivative gain ($K_d$) reduces both the overshoot and the settling time, it also produces a small change in both the rise time and steady-state error. In this example a PD controller was simulated as shown in **Figure** 3.9. The system responses are displayed in **Figure** 3.10 with different values of $K_d$, 10, 20 and 30 and with $K_p$ fixed at 300.

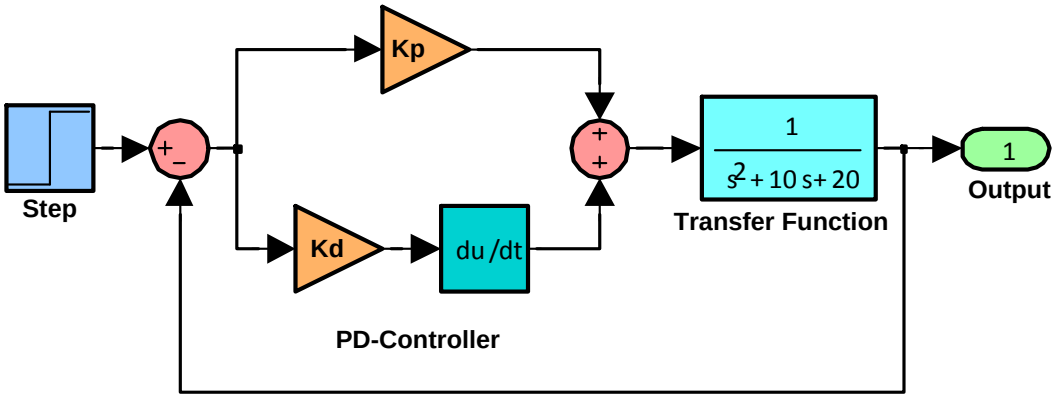



**Figure 3.9: Simulink Block Diagram of Control System with PD Controller.**

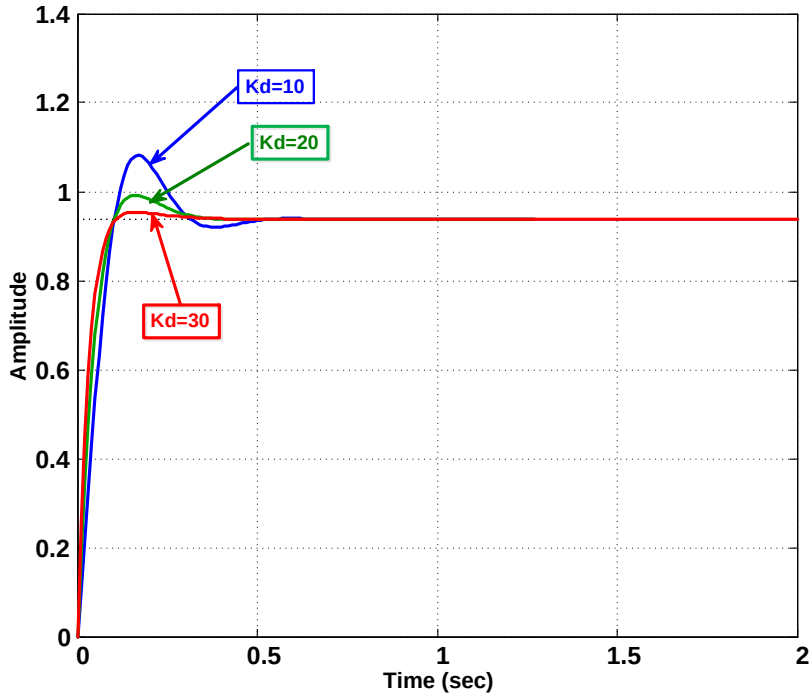



**Figure 3.10: System Responses Using PD Controller.**

### 3.2.1.5 Proportional - Integral Control – Example

The integral term decreases the rise time, increases both the overshoot and the settling time, and eliminate the steady-state error. Integral action is always used with proportional term P. **Figure** 3.11 shows the simulated PI controller and **Figure** 3.12 displays the system responses with different values of $K_i$, 70, 85 and 100 and a fixed value of $K_p$ at 30.

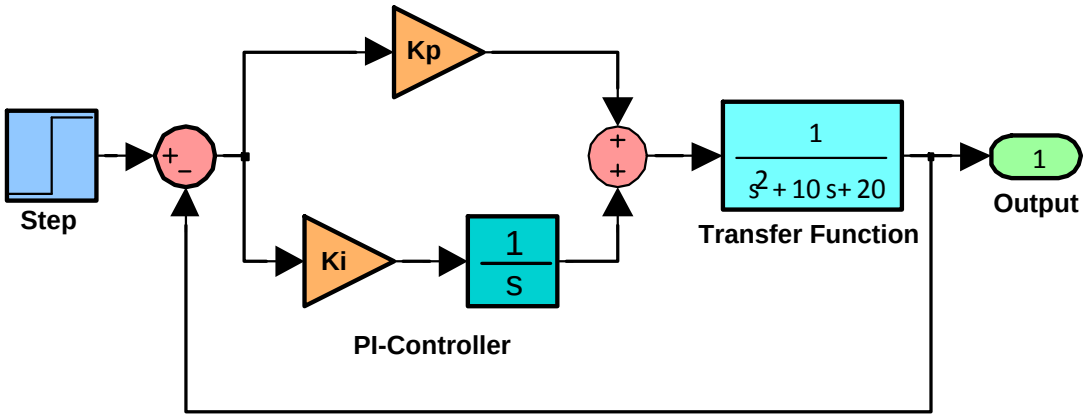



**Figure 3.11: Simulink Block Diagram of Control System with PI Controller.**

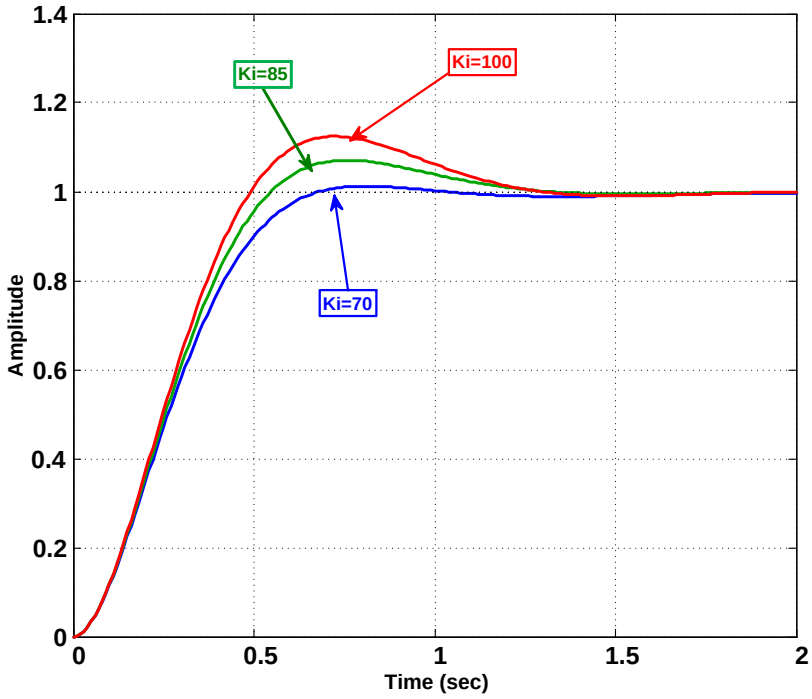



**Figure 3.12: System Responses Using PI Controller.**

In addition, there are different types of PID controller structures such as, parallel (non-interactive) and serial (interactive) that are fully explained by Vukic et al 2002 in [85]. The terms of the parallel structure have different forms as shown in **Figure** 3.13, **Figure** 3.14, **Figure** 3.15 and **Figure** 3.16. They also have different ways of dealing with the control signal. The PID control laws are given in **Equation** (3.3) and **Equation** (3.4), where **r** is the reference signal, **e** is the error signal, **u** is the control signal or plant input,

and **y** is the output signal as shown in **Figure** 3.13, **Figure** 3.14, **Figure** 3.15 and **Figure** 3.16.

$$u(t) = K\left[e(t) + \frac{1}{T_i}\int_0^t e(t)dt + T_d\frac{de(t)}{dt}\right] \tag{3.3}$$

or

$$u(t) = K_p e(t) + K_i\int_0^t e(t)dt + K_d\frac{de(t)}{dt} \tag{3.4}$$

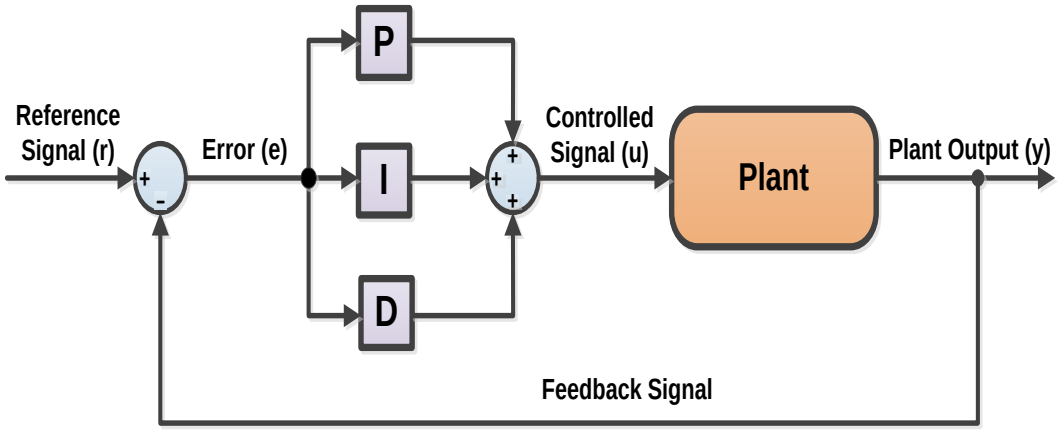



**Figure 3.13: Block Diagram of PID Controller form Parallel Structure.**

Another PID structure is shown in **Figure** 3.14 where the P and I terms of the PID controller have the error signal as input, and the derivative term is in the feedback path. Using derivative of the output signal is more robust in practical implementations [85] since the discontinuity in a step change reference signal could produce a large control signals (u). The output does not change instantaneously for a step input so a smoother signal is

produced by taking the derivative of the output. The PI-D control law is described by **Equation** (3.5), or **Equation** (3.6).

$$u(t) = K\left[e(t) + \frac{1}{T_i}\int_0^t e(t)dt - T_d\frac{de(t)}{dt}\right] \tag{3.5}$$

or

$$u(t) = K_p e(t) + K_i\int_0^t e(t)dt - K_d\frac{de(t)}{dt} \tag{3.6}$$

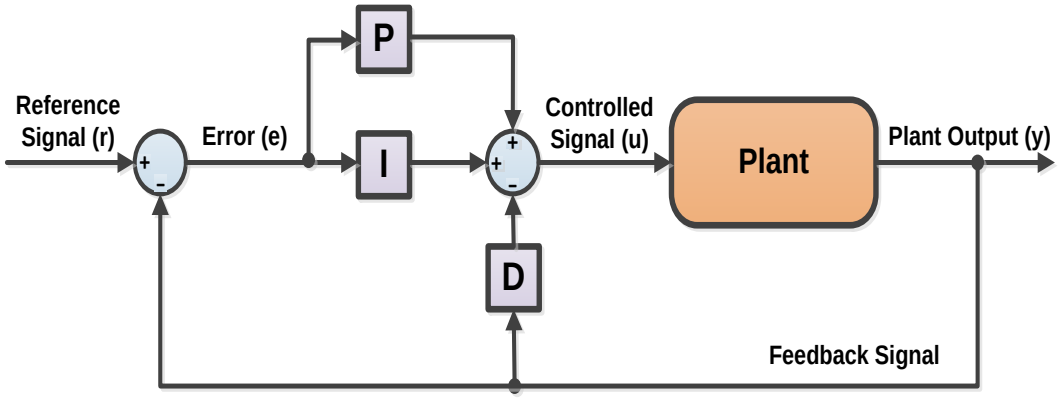



**Figure 3.14: Block Diagram of PI-D Controller form Parallel Structure.**

In the I-PD scheme shown in **Figure** 3.15, the input to the integral term (I) is the error signal. An abrupt change in the reference signal will not affect the proportional term (P) and derivative term (D), since these two terms work on the plant output (y). The control law of the I-PD is given in **Equation** (3.7), or **Equation** (3.8).

$$u(t) = K\left[\frac{1}{T_i}\int_0^t e(t)dt - y(t) - T_d\frac{dy(t)}{dt}\right] \tag{3.7}$$

or

$$u(t) = K_i \int_0^t e(t)dt - K_p y(t) - K_d \frac{dy(t)}{dt} \tag{3.8}$$

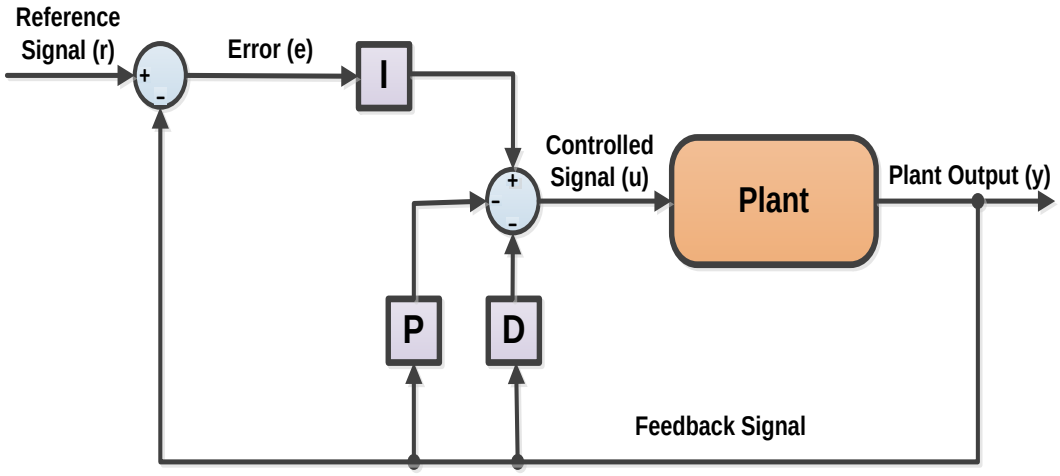



**Figure 3.15: Block Diagram of I-PD Controller Form Parallel Structure.**

The series interacting form of the PID controller is shown below in **Figure** 3.16. The control law is given by **Equations** (3.9) and (3.10).

$$u(t) = K\left[e_1(t) + \frac{1}{T_i}\int_0^t e_1(t)dt\right] \tag{3.9}$$

where

$$e_1(t) = \left[e(t) + T_d \frac{de(t)}{dt}\right] \tag{3.10}$$

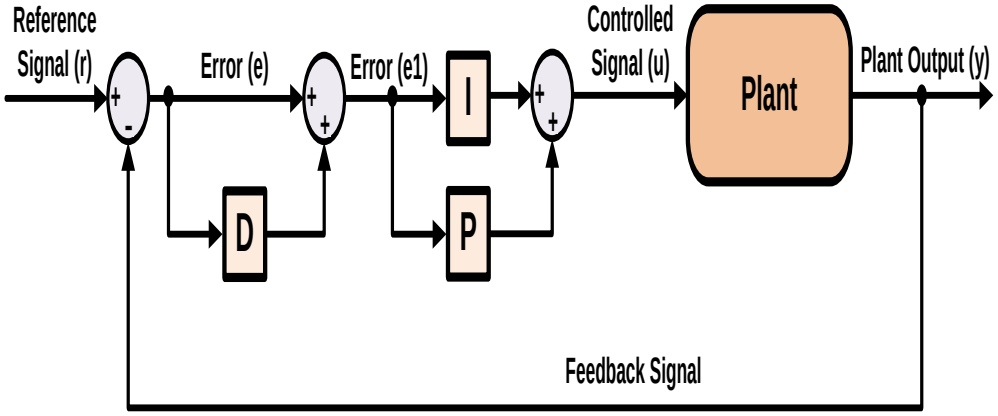



**Figure 3.16: Block Diagram of D-PI Controller Form Serial Structure.**

### 3.2.2 Internal Model Control

The structure of the IMC system consists of three terms as shown in **Figure** 2.1 of chapter two. The first term is the internal model which can be used to predict the process outputs. The second term is the internal model loop which uses the difference between the process output and the internal model output. Finally, the third term is the controller which uses the error to compute the future values of the process outputs. The difference between the output of the internal model and the process output is fed back to produce the error (e), used by the controller. This helps reduce the effect of disturbances on the system [86].

The IMC is applied to stable nonlinear systems described by linear parameter-varying models. Many researchers had proved the good performance of the Internal Mode Control method. It is an important nonlinear controlling approach to system and had been discussed by many researchers.

### 3.2.3 Adaptive Control

There are many dynamic systems having constant or slowly-varying uncertain parameters. For example robot manipulators may carry large entities with unknown inertial parameters. Fire-fighting aircraft may experience significant mass changes as they load and unload large quantities of water. Adaptive control is a solution for controlling such systems. The basic strategy in adaptive control scheme is to estimate the uncertain plant parameters or corresponding controller parameters on-line based on the measured system signals and then incorporate the estimated parameters in the control input computation. Due to this, adaptive control system can be referred as a control system with on-line parameter estimation.

Adaptive control had been introduced in the early 1950's with the design of autopilots for high-performance aircraft, which were operated at a large range of speeds and altitudes. Therefore, they faced large parameter variations. Adaptive control was suggested as a new way of automatically adjusting the controller parameters against the aircraft uncertain dynamics. It maintains consistent performance of a system in the presence of uncertainty or unknown variation in plant parameters. Since parameter perturbation occurs in many practical problems, therefore adaptive control has been successfully applied in many control applications for example in robot manipulation, ship steering, Aircraft control, Process control, power systems, biomedical engineering etc. [87].

#### 3.2.3.1 Adaptive Controller Design

An adaptive controller is different from conventional controller (non-adaptive) in that the controller parameters are variable, and there is a certain mechanism for adjusting these parameters on-line. Generally, adaptive controller is superior to robust controller in dealing with parameters uncertainties. It requires slight or no a priori information about the unknown parameters, whereas a robust controller usually needs sufficient information about parameter bounds. However, a robust controller has some significant features which an adaptive controller does not contain, such as its ability to deal with disturbances and unmodeled dynamics. Such characteristics essentially are combined with adaptive control to increase robustness. There are mainly two techniques for constructing adaptive controllers: one is the model-reference adaptive control (MRAC) method and the other is the self-tuning method. The block diagram of MRAC scheme is shown in the **Figure** 3.17. It consists of four parts. The plant containing unknown parameters may be linear or non linear.

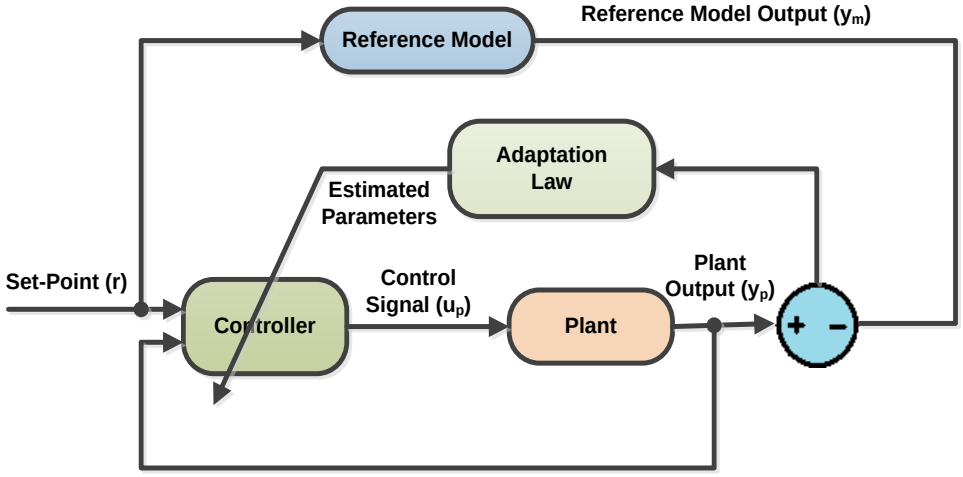



**Figure 3.17: A model-reference adaptive control.**

The reference model is used to specify the desired output of the control system. The feedback control law should be designed in such a way that when the plant parameters are exactly known, the corresponding controller should make the plant output identical to that of the reference model. In case when the plant parameters are unknown, the adaptation mechanism will adjust the controller parameters so that perfect tracking is asymptotically achieved. The adaptation law searches for parameters such that the response of the plant under adaptive control becomes the same as that of the reference model. The main objective of the adaptation is to make the control system stable and to make the tracking error converge to zero. **Figure** 3.18 illustrate the schematic structure of self-tuning approach for constructing adaptive controllers. In this approach the controller performs simultaneous identification of the plant. First, the parameters of the plant are estimated, and then the controller parameters are computed.

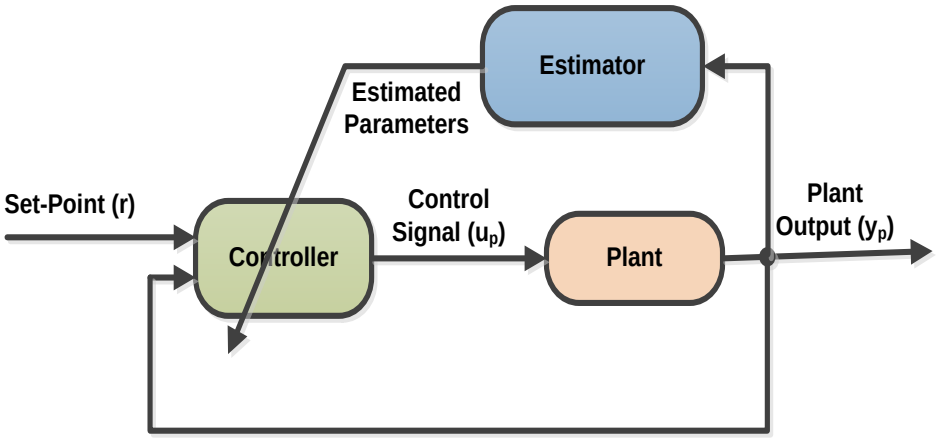



**Figure 3.18: Self tuning control system.**

The design of adaptive controller is slightly different from the conventional one. In the conventional control, the controller structure is chosen first and then the parameters of the controller are computed using the known parameters of the plant, whereas in adaptive control being the plant parameters are unknown, the parameters of the controller are provided using the adaptation law. Briefly, the adaptive controller is usually designed using the following three steps:

1. Choose a control law containing variable parameters.
2. Choose an adaptation law for adjusting those parameters.
3. Analyze the convergence properties of the overall control system.

In this thesis we investigated adaptive strategies for hemodynamic variable control using one and more drugs.

#### 3.2.3.1.1 Model Reference Adaptive Control

**Figure** 3.19 show the general structure of MRAC. The adaptive law of this controller has been presented by Sobel, Kaufman and Mabius (1982)

[88] and is defined by **Equation** (3.11), **Equation** (3.12), **Equation** (3.13), **Equation** (3.14), **Equation** (3.15), and **Equation** (3.16).

$$u_p = k_y(t) \times y_m(t) + k_u(t) \times u_m(t) + k_e(t) \times [y_m(t) - y_p(t)] \quad (3.11)$$

where, $u_p$ represent the control signal, ym is the outputs of reference model, um represent the set-point or desired value and $y_p$ is the plant outputs The controller's parameters which represent by $k_y$, $k_u$ and $k_e$, these parameters being adaptive, see **section** 5.3 in **chapter** 5 for more details. The objective is to make the controlled output $y_p$ track the output of reference model $y_m$.

$$\big(y_m(t) - y_p(t)\big) = e(t)$$

where, e(t) is the tracking error.

$$u_p = k_r(t) \times r(t) \quad (3.12)$$

$$\text{where,} \qquad r(t) = \begin{bmatrix} e(t) \\ y_m(t) \\ u_m(t) \end{bmatrix}$$

and

$$k(t) = [k_e, \quad k_y, \quad k_u] \quad (3.13)$$

$\therefore$

$$k_r(t) = k_p(t) + \hat{k}_i(t) \quad (3.14)$$

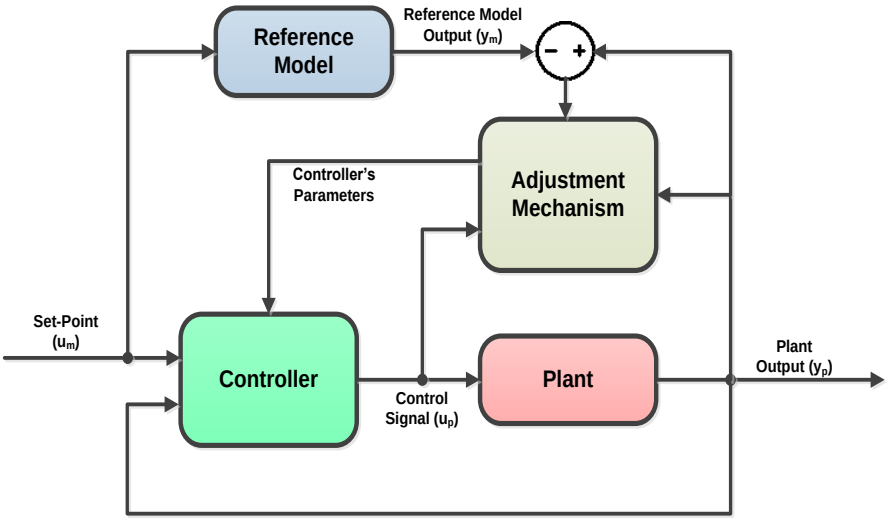



**Figure 3.19: Block Diagram of General Structure of MRAC.**

The adaptive gain vector $k_r$ (t) in **Equation** (3.14) is obtained as a combination of proportional and integral gains as follows:

$$k_p(t) = e(t) \times r^T \times A \tag{3.15}$$

$$k_i(t) = e(t) \times r^T \times B \tag{3.16}$$

In **Chapter** 5 we designed and implemented a multivariable MRAC in order to maintain the hemodynamic variables MAP and cardiac output (CO).

#### 3.2.3.1.2 Multiple Model Adaptive Control

The control of dynamic systems with large uncertainties has received great attention by both control theorists and engineers. It is known that the system with unknown time invariant or slowly time varying parameters can get good performance by using conventional adaptive controller. But when the system boundary conditions change, the subsystem fails or a large external disturbance occurs, the system parameters will change immediately and the presence of the large parameter errors will generally result in a slow

reaction, slow convergence, poor transient response and even instability [89]. In order to solve this problem, an MMAC system has been implemented by Narendra and Balakrishnan in 1997 and 1994. The multiple models have been incorporated to improve the transient response as well as efficiency of the system [90] and [91].

#### 3.2.3.1.3 Self-Tuning Control

Self-tuning or self-adapting systems of automatic control are systems whereby adaptation to randomly changing conditions is performed by means of automatically changing parameters or via automatically determining their optimum configuration. In any non-self-tuning automatic control system there are parameters which have an influence on system stability and control quality and which can be tuned. If these parameters remain constant whilst operating conditions (such as input signals or different characteristics of controlled objects) are substantially varying, control can degrade or even become unstable. Manual tuning is often unwieldy and sometimes impossible. In such cases, not only is using self-tuning systems technically and economically worthwhile, but it could be the only means of robust control. Self-tuning systems can be with or without parameter determination [92].

### 3.2.4 Fuzzy Control

Fuzzy controllers are very simple conceptually. They consist of an input stage, a processing stage, and an output stage, the consisting of these

stages has shown in **Figure** 3.20. The input stage maps sensor or other inputs, such as switches, thumb-wheels, and so on, to the appropriate membership functions and truth values. The processing stage invokes each appropriate rule and generates a result for each, then combines the results of the rules. Finally, the output stage converts the combined result back into a specific control output value [93].

In addition, fuzzy logic system design is not based on the mathematical process model. Fuzzy controllers designed using fuzzy logic implement human reasoning that has been programmed into membership functions, fuzzy rules and rule interpretation. A fuzzy logic controller involves four main stages: fuzzification, rule base, inference mechanism and defuzzification as shown in **Figure** 3.21.

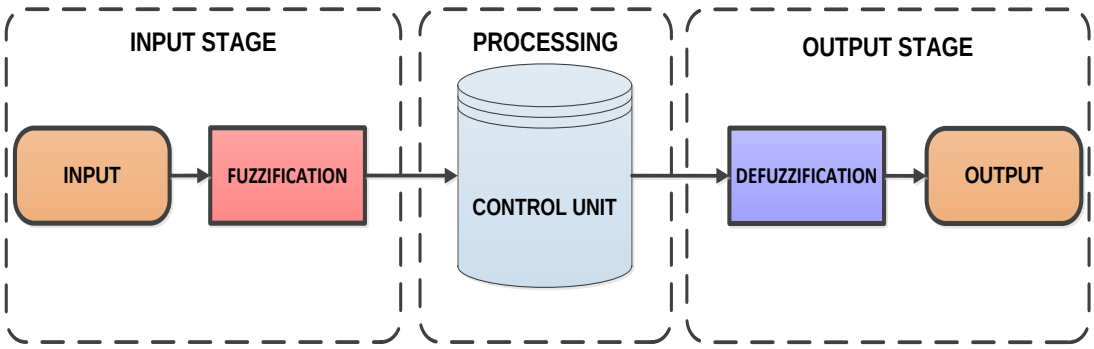



**Figure 3.20: Block Diagram of General Structure for Fuzzy Control.**

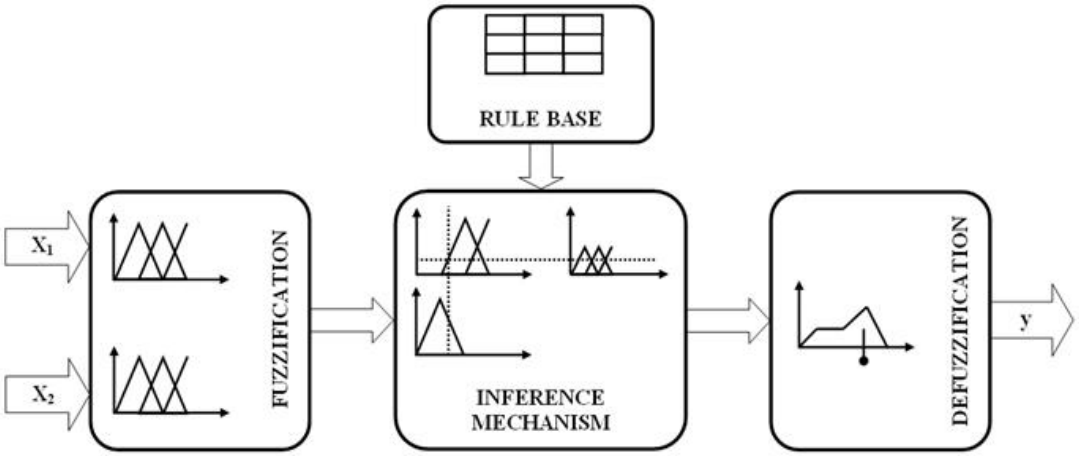



**Figure 3.21: General structure of a fuzzy controller.**

The fuzzification and the defuzzification stages are needed to convert and reconvert real world crisp signals into fuzzy values and vice versa. The inference mechanism determines the matching degree of the current fuzzy input with respect to each rule and decides which rules are to be fired according to the input field. Next, the fired rules are combined to form the control actions [94].

### 3.2.5 Neural Network

In this section we will present the general definition of a Neural Network. A Neural network is an interconnected system of simple elements called units or nodes. The elements functionality is based on the biological neuron. A biological neuron consists mainly of three parts: *dendrites*, *soma*, and *axon* as illustrated in **Figure** 3.22. The human brain comprises an estimated 100 billion neurons. The human nervous system can be divided into three stages as represented in block diagram in **Figure** 3.23.

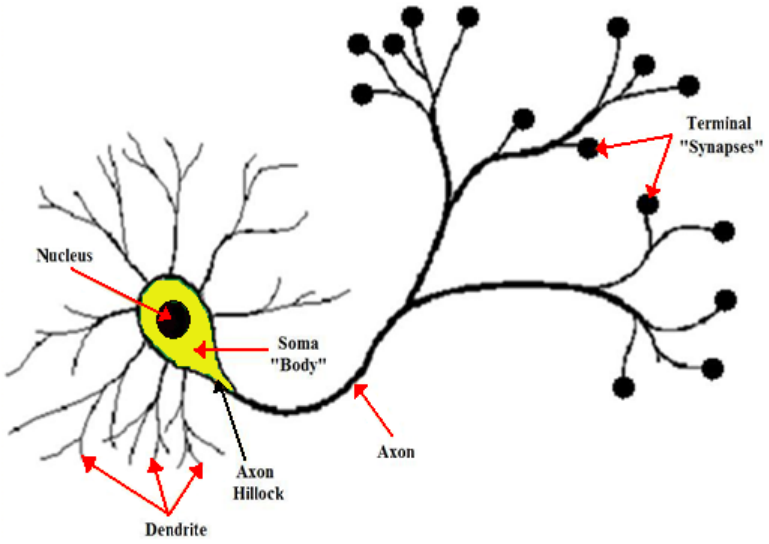



**Figure 3.22: Schematic of Biological Neuron.**

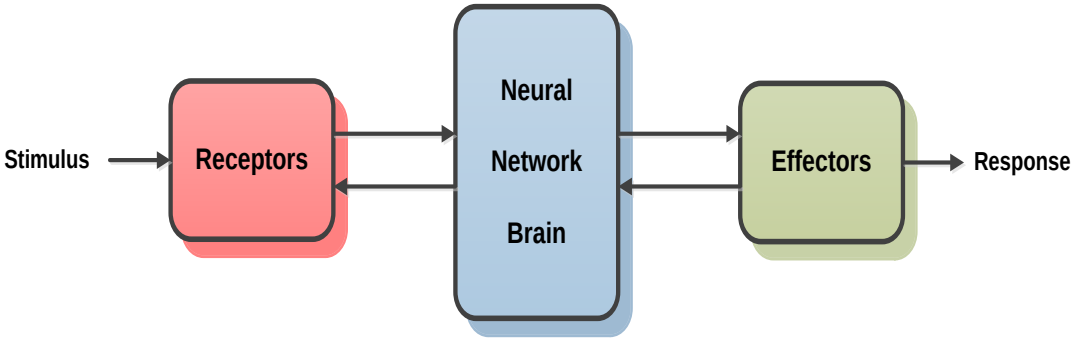



**Figure 3.23: The Stages of Nervous System.**

The inter unit connection strengths or weights used to store the processing ability of the network, are obtained by the process of adaptation to or learning from a set of training types [95].

The Artificial Neural Network (ANN) has been widely used in many fields such as process control, diagnostics, sensory prediction, identification, character recognition, robot vision, and forecasting, due to its ability to capture complex patterns present in the data. The ANN is an Information processing model that is inspired by the biological nervous systems, such as the brain which process information. ANNs, like humans, learn by example

via training. An ANN is configured to work for a particular application, such as pattern recognition or classification of data, through a process of learning. The ANN is learns as in biological systems which involve adjustments to the synaptic connections that exist between the neurones [96].

The neural network is composed of a number of node elements, which are connected together to produce either a single layer or multiple layers. These node elements are utilized in neural networks depending on the type of network considered. One commonly encountered model is a form of the McCulloch-Pitts neuron, as shown in **Figure** 3.24.

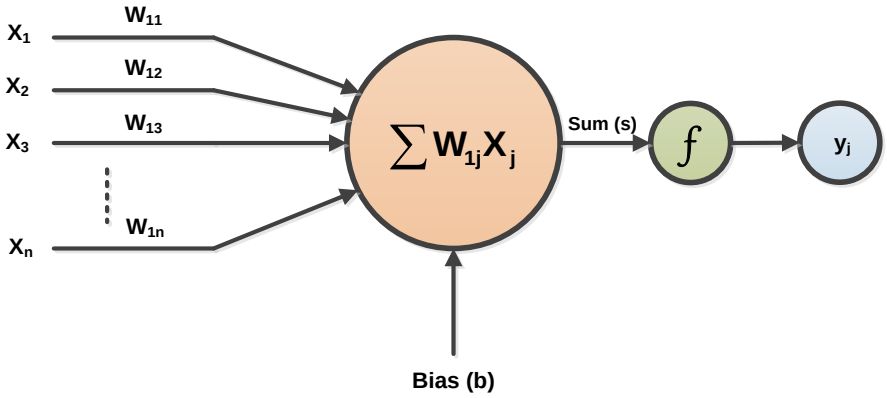



**Figure 3.24: Block Diagram of McCulloch-Pitts Neuron.**

Mathematically, the input signal $\mathbf{X_i}$ is multiplied by a weight parameter $\mathbf{W_{ij}}$ and all weighted input signals are added to give the total input to the neuron as defined by **Equation** (3.18) and the output as defined by **Equation** (3.20). The bias **b** is a special weight which can be treated as a weight whose input is always equal to 1.

$$s = W_{11}x_1 + W_{12}x_2 + W_{13}x_3 + \cdots + W_{1n}x_n \tag{3.17}$$

$$s = \sum_{i=1}^{n} W_{in} x_n \tag{3.18}$$

$$y_j = f(w_{11}x_1 + w_{12}x_2 + w_{13}x_3 + \cdots + w_{1n}x_n + b) \tag{3.19}$$

$$y_j = f\left(\sum_{i=1}^{n} W_{ij} x_j\right) \tag{3.20}$$

The performance of the trained network depends on the learning algorithm, the number of layers, neurons, connections and on the type of transfer functions computed by each neuron. To avoid over and under fitting of the data the bias variance should be balanced by matching the complexity of the network to the complexity of the data. The transfer functions which commonly used are hard-limit, log-sigmoid and linear transfer functions, these have presented in **Table** 3-3.

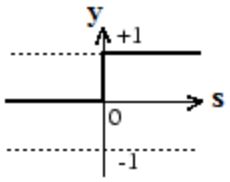
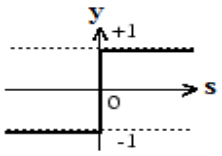
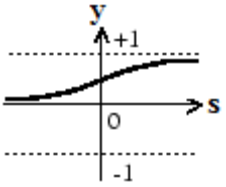
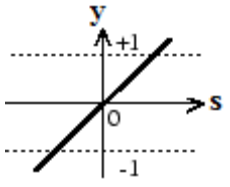
#### 3.2.5.1 Advantages

- A neural network is able to perform tasks that a linear program cannot.
- Because of its parallel structure, a neural network can still function even when one of its elements fails.
- A neural network is able to work by learning and does not need to be reprogrammed.
- There are various neural network algorithms which cover a wide range of applications.

### 3.2.5.2 Disadvantages

- A neural network requires training to operate.
- A neural network needs to be emulated because its architecture is different from the architecture of microprocessors.
- High processing time for large neural networks.

**Table 3-3: Types of Transfer Function.**

| TRANSFER FUNCTION | FIGURE |
|---|---|
| Hard Limit transfer function:<br>$y = 0 \quad \text{if} \quad s < 0$<br>$y = 1 \quad \text{if} \quad s \geq 0$ |  |
| Symmetrical (Hard Limit) transfer function:<br>$y = -1 \quad \text{if} \quad s < 0$<br>$y = +1 \quad \text{if} \quad s \geq 0$ |  |
| Log-Sigmoid transfer function<br>This transfer function takes the input and produces an output in the range 0 to 1, according to the expression:<br>$y = \frac{1}{1 + e^{-s}}$ |  |
| Linear transfer function:<br>y = s |  |

#### 3.2.5.3 Training Neural Network

Among the existing tuning techniques, the well-known Ziegler-Nichols tuning method can be implemented to tune the parameters of PID controller. This kind of method is simple and gives fixed values of the parameters. A controller with fixed parameters is not capable of responding to variations in system dynamics and changes in operating conditions. In blood pressure control, patients have different sensitivities and responses to drugs. We need a controller that is able to perform well for all types of patients.

This chapter investigates the use of neural networks in adaptive control systems. Adaptive control solves the problem of the sensitivity to variation in the plant parameters. In the case of neural adaptive control, the controller parameters are changed by a neural network trained off-line. The training patterns are obtained using any design method of the controller for many different values of the plant parameters. A useful tool to train any neural adaptive controller has been developed. In this chapter we have investigated how to find the optimal way to make the PID controller able to control the multiple-drug delivery system online to regulate MAP and CO by administering two drugs. The Matlab Neural Network Fitting Tool (NNFT) tool was used to train the network [97] to make the PID controller adaptive. A neural network can be trained to perform a particular function by adjusting the values of the connections (weights) between elements. The neural network structure and training will be presented in chapter six.

## 3.3 Algorithm Optimisation

A non-linear system is one of the reasons for the complexity of the tuning process of algorithm. Commonly, one can obtain controller settings with the traditional linear analysis methods and then utilizes the settings by implementing trial and error methods during a mission. Employing GAs methods gives the best values of the system parameters. Matlab Simulink Response Optimization Tools (SROT) [48] was used in this thesis to obtain optimal parameters values of the controllers.

### 3.3.1 Genetic Algorithms

Genetic Algorithms (GAs) are adaptive heuristic search algorithm based on the evolutionary ideas of natural selection and genetic. In different fields such as business, engineering, and science, these methods have been applied successfully to obtain suitable solutions for problems [98]. These methods are generally able to find optimal solution of the problems in suitable amounts of time.

Genetic algorithms are part of development computing, which is a quickly growing area of artificial intelligence. GAs is a stochastic universal search method which mimics the process of natural evolution. It has been classified as one of the methods used for optimization. It is adapted from Darwin's theory of evolution. The algorithm starts with a set of hypothetical solutions and represented by chromosomes, called population. The solutions which obtained from one population are taken and used to structure a new

population. This is motivated by a hope, that the new population which has been considered is better than the previous one. The solutions which are selected are considered as new solutions (offspring) and chosen according to their fitness. The more suitable solutions have more chances to reproduce [99]. In order to produce offspring, the process starts with a set of randomly generated solutions then pairs of them recombined at random to produce offspring. The next generation is produced by keeping the best offspring and parents.

Ordinarily, the population is initialized with N random strings (Chromosomes). The randomly generated initial population is represented by p(1). If p(t) represents the population at time t then the new population will be p(t+1) and it is created by applying a set of genetic operation as reproduction. There is a fitness value for each chromosome in a new population. As the chromosome has some parameters then the fitness value may be constricted from some parameters in each chromosome. The general genetic algorithm has the following structure [100, 101]:

- Selection
- Crossover
- Mutation

#### 3.3.1.1 Selection

The Selection is a genetic operator which selects the chromosome from the current generation's population for inclusion in the next generation's population. Before inserting the chromosome in the next generation's

population, the chromosomes which have been selected may undergo crossover and/or mutation that depend on the probability of crossover and mutation. In this case the offspring chromosomes are actually the ones that have been inserted into the next generation's population.

#### 3.3.1.2 Crossover

Producing a new chromosome (offspring) needs to combine (mate) two chromosomes (parents) and this process is accomplished by the genetic operator called crossover. The idea behind crossover is that the new chromosome may be better than both of the parents if it takes the best characteristics from each of the parents. Crossover occurs during evolution according to a user-definable crossover probability.

#### 3.3.1.3 Mutation

The modification of one or more gene values in a chromosome from its initial state is done by mutation, which results in a completely new gene values being added to the gene pool. With these new gene values, the genetic algorithm may be able to arrive at a better solution than was previously possible. This part is an important part of the genetic search. It is helpful to stop the population from stagnating at any local optima. Mutation happens during evolution according to a user-definable mutation probability. This probability should usually be set fairly low (0.01 is a good first choice). If it is set too high, the search will turn into a primitive random search.

#### 3.3.1.4 Working principles of GAs

Initialization: The implementation of any genetic algorithm starts by generating an initial population. In many cases the initial population is generated randomly.

Selection: Selection operator is applied to the current population to create an intermediate one. In the first generation, the initial population will consider as the intermediate one, while in the next generations this population is created by the application of the selection operator.

Generation (Crossover–Mutation): In order to create the next generation, crossover and mutation operators are applied to the intermediate population to create the next population. Crossover is a reproduction operator, which forms a new chromosome by combining parts of each of the two parental chromosomes. Mutation is a reproduction operator that forms a new chromosome by making (usually small) alterations to the values of genes in a copy of a single parent chromosome. The process of going from the current population to the next population constitutes one generation in the evolution process of a genetic algorithm. If the termination criteria are satisfied the procedure stops, otherwise, it returns to the measure fitness step, as shown in **Figure** 3.25.

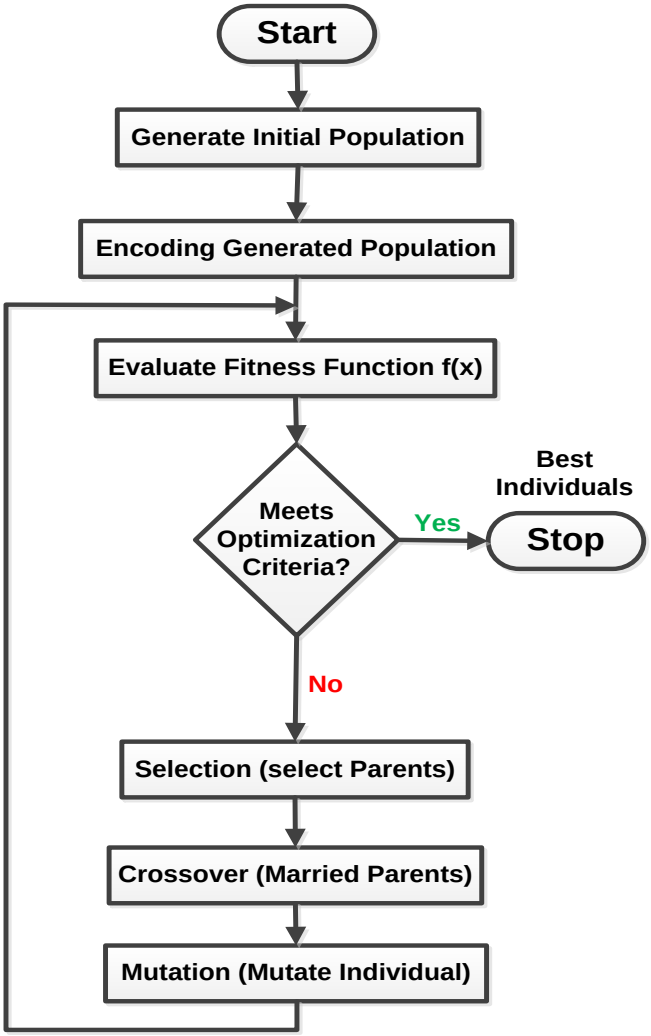



**Figure 3.25: Flowchart of Genetic Algorithm.**

### 3.3.1.5 Main advantages:

- GA can be used to solve any optimisation problem described with the chromosome encoding.
- It is able to solve any problems with multiple solutions.
- The technique can be used to solve problems that are non-parametric, non-continuous, non- differential, and even multi-dimensional in nature.
- GA is very easy to understand and does not require a mathematical model.

#### 3.3.1.6 Main disadvantages:

- The GA approach uses extensive computational resources
- There are problems that cannot be solved by GA. This is due to poorly known fitness functions which generate bad chromosome blocks.
- With GA, there is no guarantee that the answer converges to global optimum.
- The gap between optimisation response time is longer than the conventional gradient method. This limits its use in real-time applications.
- In addition, the genetic algorithm applications which are used in real time controls are limited because of random solutions and convergence.

# Chapter 4.

## CONTROL SCHEMES FOR SINGLE-INPUT SINGLE-OUTPUT (SISO) PATIENT RESPONSE MODEL

### 4.1 Introduction

Postoperative hypertension is a well-known complication of cardiac surgery in patients. The operation has been done at the Milton **S.** Hershey Medical Centre for 25 patients who have coarctation of the aorta. The report revealed a 56% incidence of paradoxical hypertension in the first time of postoperative period. The sympathetic nervous system is responsible for up- and down-regulating many homeostatic mechanisms. One of the sympathetic nervous system responsibilities is the initial phase of the paradoxical hypertension after surgery. In fact, many studies have tried to find out the reasons of the increase in the blood pressure in postoperative patients [1, 2].

SNP is a powerful anti-hypertension medicine. The action of sodium nitroprusside is one of direct dilatation of the vasculature, and it acts predominately on the tonic smooth muscle of the blood vessels. It must be given intravenously with careful manipulation of the infusion rate to avoid toxic SNP effects [3, 4]. The infusion of SNP and its effect on biological system presents a real problem in postoperative patients [6-9]. The automatic control of blood pressure in postoperative patients is desirable for

effective patient's care and to avoid drug overdose [7]. There are large variations in the types of patient's response to drugs. These models have been used to design several controllers [8, 9]. Slate et al., have determined the performance criteria of automatic control of blood pressure using the SNP drug [7, 42].

In this chapter, we propose to use two types of control strategies; an IMC and a PID controller. The aim is to compare the optimal performance of these two approaches. We used the GAs searching method as one of the SROT methods [48]. GAs is used to optimise the tuning parameters of the IMC and PID controllers [50]. Design and analysis for time-varying control systems are difficult and very often complex algorithms would be necessary for estimating the system parameters and for on-line tuning of the controller. An accurate estimation of the system parameters, especially time-delays, is the key for system stability and performance [50]. The IMC can be tuned to minimise the disturbance using only one tuning parameter, this parameter is K as shown in [8]. The PID controller can be tuned using three parameters, $K_p$, $K_i$ and $K_d$. Optimal tuning of controller's parameters are used to achieve optimal drug infusion rate.

Researchers have conducted many studies on modelling and/or control of abnormal blood pressure in patients. This chapter presents a comparison of performances between IMC and PID controllers. The parameters of these controllers have been optimised by using GAs

optimization technique. The resulting controllers are tested on different models of patient's sensitivity to SNP.

## 4.2 SISO Patient Response Model

Slate et al. [26, 42] have performed extensive research on patients to obtain the suitable model which can present the change in MAP to the infusion rate of drug. The model of patients' response to the SNP is described by **Equation** (4.1). This is a linear first-order transfer function, obtained using correlation analysis with a pseudo-random binary signal (PRBS).

$$G_p(s) = \frac{\Delta P(s)}{I(s)} = \frac{Ke^{-T_i s}(1 + \alpha e^{-T_c s})}{\tau s + 1} \tag{4.1}$$

where, the $\Delta P(s)$ refers to the change in blood pressure in units of (mmHg), and the $I(s)$ is the drug infusion rate measured in units of (ml/h), K is the patient's sensitivity to the drug in units of (mmHg/ml/h), K(1+α) is the steady-state gain or dose response, α is the fraction of re-circulation constant, $\tau$ represents the system time constant in units of (s), $T_i$ is the initial transport delay in units of (s), and $T_c$ is the re-circulation time delay in units of (s).

MATLAB SIMULINK© tool box was used [102, 103] to simulate the model in **Equation** (4.1), as shown in **Figure** 4.1.

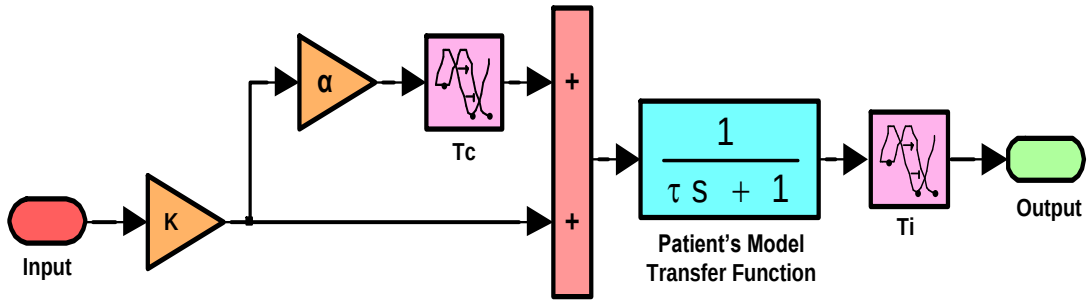



**Figure 4.1: Block Diagram of Simulink Model of Patient Response.**

During clinical evaluations of the patient model, it was observed that several disturbances could have an effect on the patient's behaviour, which could lead to an increase/decrease in the patient's blood pressure. Slate et al. modelled the disturbance [7] as shown in **Figure** 4.2.

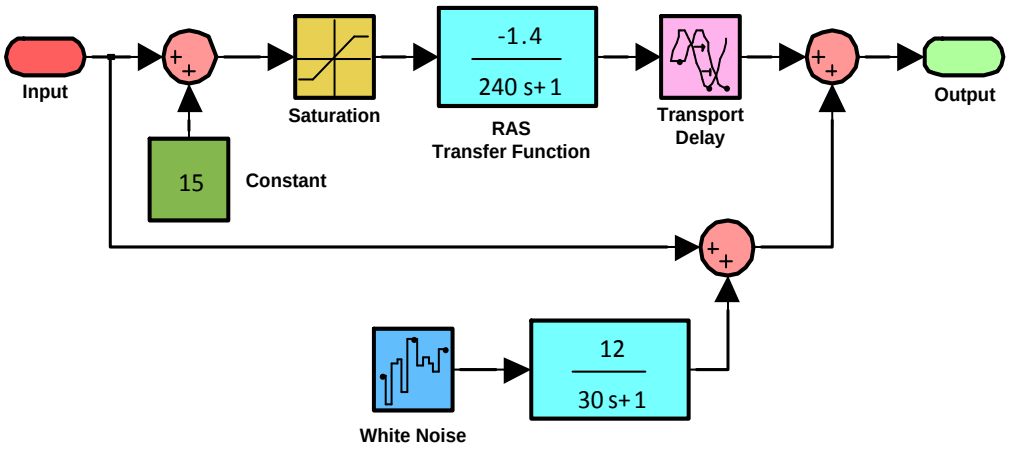



**Figure 4.2: Block Diagram of Simulink Models of Disturbances.**

The random fluctuations and patient's reflex response due to the drop in blood pressure are the main source of disturbance [7]. The disturbance is made up of two components:

- ❖ Disturbances due to stochastic activity and respiration effects.
- ❖ The patient's reflex response due to a drop in the blood pressure.

The proposed controllers have been designed to achieve the required performance for different types of patients as given by the parameter variation shown in **Table** 4-1. The validation of the performance of the controllers is checked following two steps. In the first step the controllers are applied to three different types of patients, a nominal, sensitive and insensitive patient to the drug without disturbances. These will show that the controllers can meet the performance specification for which it was designed. In the second step the controllers have been applied to three different types of patients under the influence of disturbances that can have a nonlinear character as proposed by Slate et al. (1982) [7].

**Table 4-1: The Patient's Model Parameters Values.**

| Parameters | Unites | Sensitive | Nominal | Insensitive |
|---|---|---|---|---|
| Steady-state gain - K(1+α) | mmHg/(ml/h) | - 9 | - 0.714 | - 0.178 |
| Initial transport delay - Ti | s | 20 | 30 | 60 |
| Re-circulation time - Tc | s | 30 | 45 | 75 |
| Re-circulation - α | - | 0 | 0.4 | 0.4 |
| System time constant - τ | s | 30 | 40 | 60 |

## 4.3 Controllers Optimization and Results

A drug infusion controller should be designed to work well in a real-time environment for a wide range of patients. The proposed controller structure should be as simple as possible to solve the drug infusion problem.

The following performance criteria introduced in [7] were used to evaluate the performance of our controllers:

- Setpoint is -30 mmHg.
- Settling time should be less than 1200 s.
- Overshoot between 8 to 10 mmHg.
- No steady-state offset but with an error tolerance of 5 mmHg.

### 4.3.1 IMC Controller

The structure of the IMC system consists of three terms as shown in **Figure** 2.1 in chapter two. The first term is the internal model which can be used to predict the process outputs. The second term is the internal model loop which uses the difference between the process output and the internal model output. Finally, the third term is the controller which uses the error to compute the future values of the process outputs.

The difference between the output of the internal model and the process output is fed back to produce the error, e, used by the controller. This helps to reduce the effect of disturbances on the system [86].

We implemented the IMC which was first developed by Garcia et al. [46] on the patient model proposed by Slate et al. [26, 42]. The IMC has been applied to control blood pressure in [47, 49]. In [8] the analysis of the model parameters has shown that the model gain K, (see **Figure** 4.3 below) is the only parameter which affects the stability of the control system.

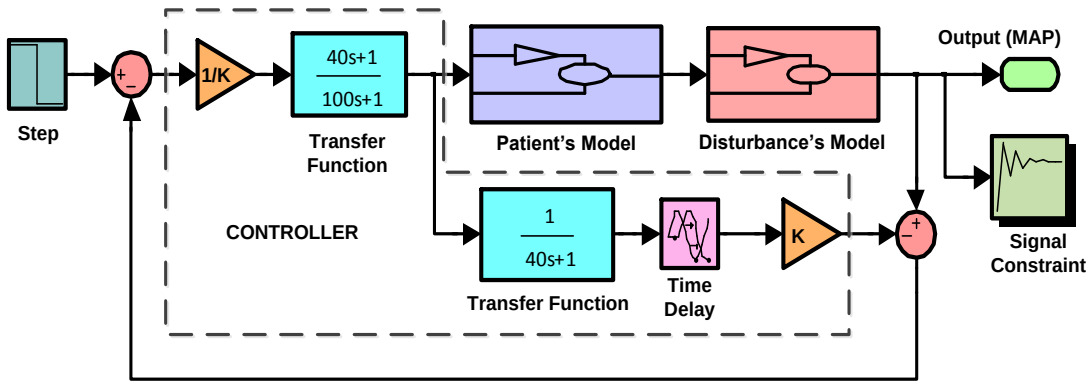



**Figure 4.3: Full Control System with (GAs) Optimisation Technique.**

In this chapter we used the GAs optimisation search technique as one of the SROT methods to find the optimal value of the parameter "K" that satisfies the performance criteria and achieves the desired level of MAP (-30 and -25 mmHg) with optimal values of infusion rate, with and without disturbance as shown in **Table** 4-2, **Table** 4-3, **Table** 4-4 and **Table** 4-5 respectively.

**Table 4-2: IMC's Gain with Disturbance and Setpoint is -30 mmHg.**

| Patient's Type | Parameter "K" | SNP (ml/h) | MAP (mmHg) |
|---|---|---|---|
| Sensitive | - 4.5437 | 7.996 | -30.30 |
| Nominal | - 0.5746 | 72.08 | -30.22 |
| Insensitive | - 0.2792 | 289.3 | -30.14 |

**Table 4-3: IMC's Gain without Disturbance and Setpoint is -30 mmHg.**

| Patient's Type | Parameter "K" | SNP (ml/h) | MAP (mmHg) |
|---|---|---|---|
| Sensitive | - 5.5985 | 3.333 | -30 |
| Nominal | - 1.8001 | 30.01 | -30 |
| Insensitive | - 0.4568 | 120.4 | -30 |

The system has been tested on different patient's model in presence of disturbances with three types of sensitivities to drugs (sensitive, nominal and insensitive patients) with desired level of blood pressure as -30 mmHg.

**Table** 4-2 and **Table** 4-3 illustrate the disturbances effects on patient's blood pressure, due to that the infusion rates of the drugs increases and decreases depending on the desired level of blood pressure. **Figure** 4.4, **Figure** 4.6 and **Figure** 4.8, demonstrate the simulation results for sensitive, nominal and insensitive patient's responses to SNP, respectively. And **Figure** 4.5, **Figure** 4.7 and **Figure** 4.9 show the infusion rates for each patient. From these simulation results we have observed that the initial value of infusion rates is different from patient to patient. If the patient is sensitive the initial infusion rate is smaller compared to nominal and insensitive patients as shown in **Figure** 4.5 which has a value 2.641 ml/h, in **Figure** 4.9 the initial value of infusion rate for insensitive patient is 42.98 ml/h. The effect of disturbances on the sensitive patient's response and infusion rate has shown in **Figure** 4.10 and **Figure** 4.11.

**Table 4-4: IMC's Gain with Disturbance and Setpoint is -25 mmHg.**

| Patient's Type | Parameter "K" | SNP (ml/h) | MAP (mmHg) |
|---|---|---|---|
| Sensitive | - 4.5437 | 7.439 | - 25.3 |
| Nominal | - 0.5746 | 67.07 | - 25.21 |
| Insensitive | - 0.2792 | 269.2 | - 25.14 |

**Table 4-5: IMC's Gain without Disturbance and Setpoint is -25 mmHg.**

| Patient's Type | Parameter "K" | SNP (ml/h) | MAP (mmHg) |
|---|---|---|---|
| Sensitive | - 5.5985 | 2.778 | - 25 |
| Nominal | - 1.8001 | 25.01 | - 25 |
| Insensitive | - 0.4568 | 100.3 | - 25 |

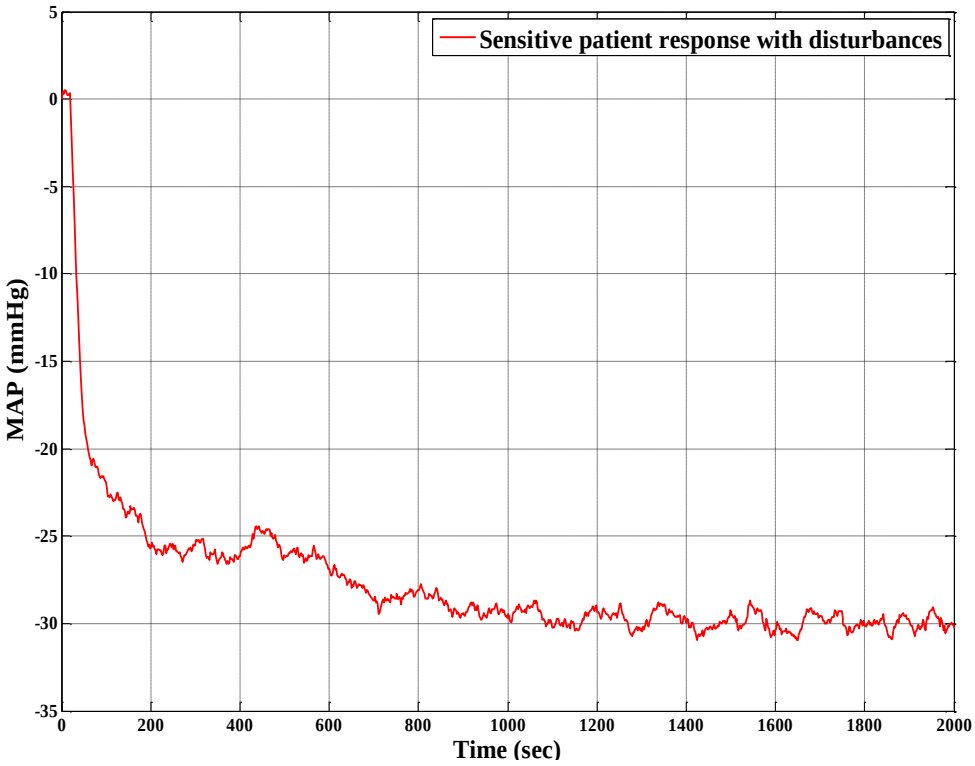



**Figure 4.4: Sensitive Patient's Response using IMC.**

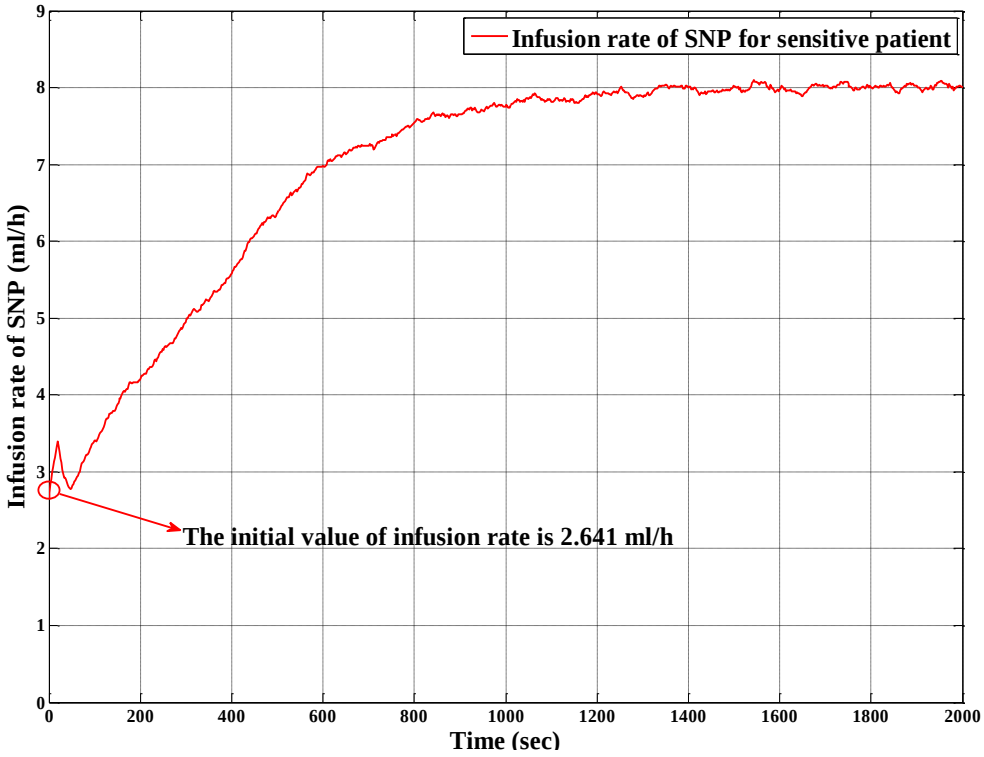



**Figure 4.5: Sensitive patient's infusion rate using IMC.**

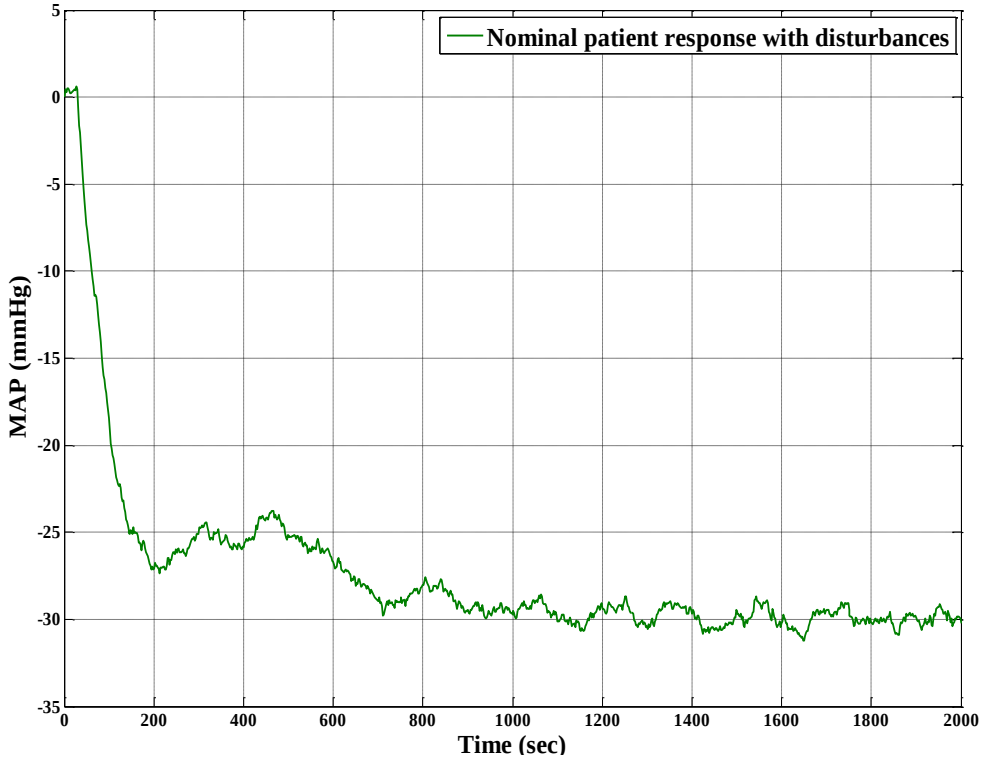



**Figure 4.6: Nominal patient's response using IMC.**

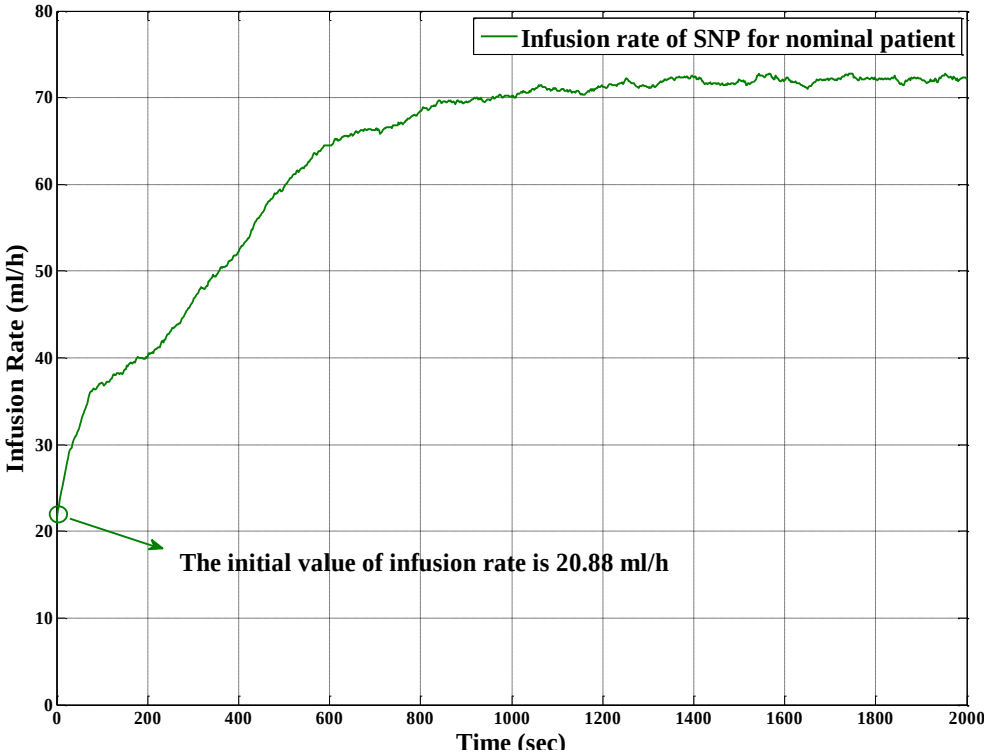



**Figure 4.7: Nominal Patient's Infusion Rate using IMC.**

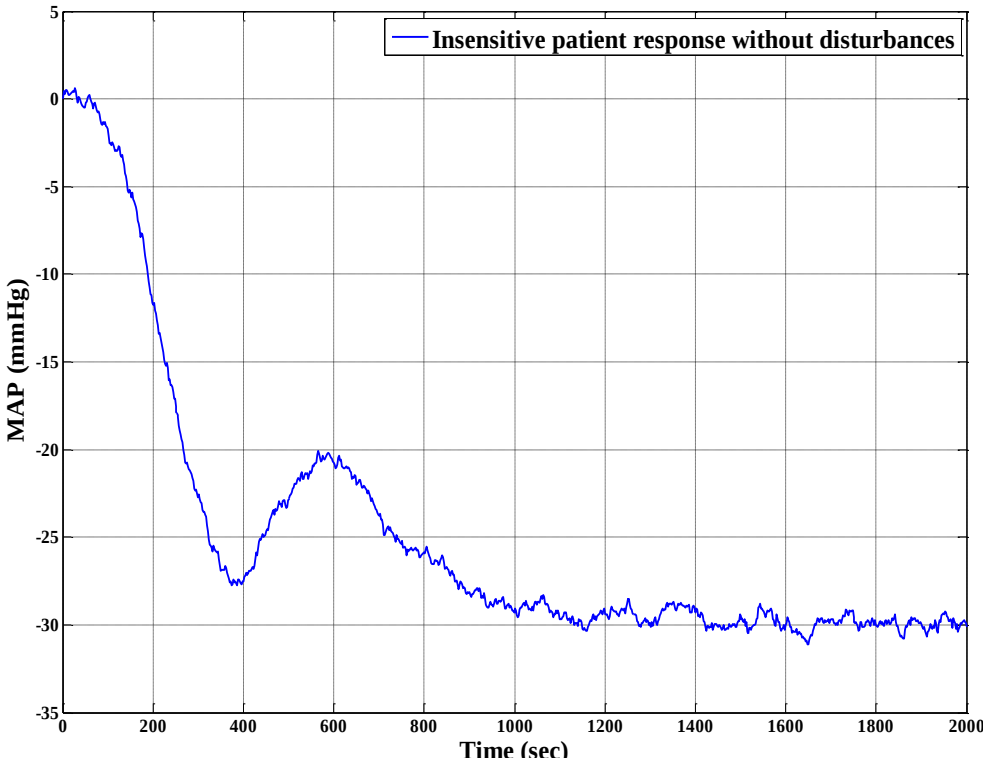



**Figure 4.8: Insensitive Patient's Response using IMC.**

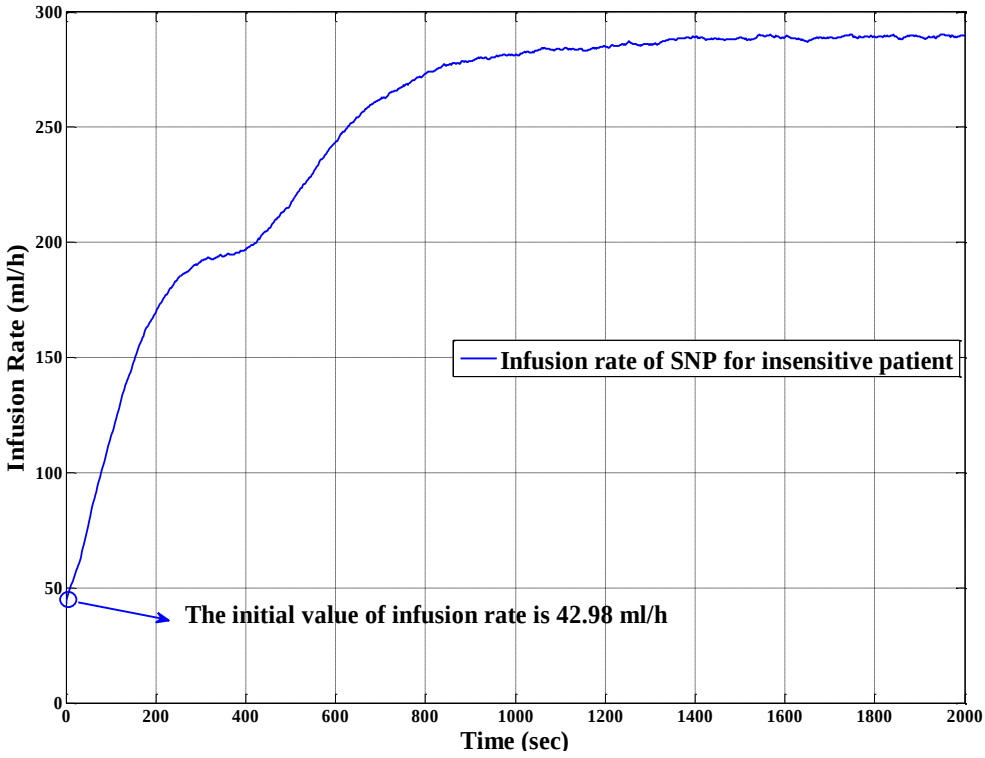



**Figure 4.9: Insensitive Patient's Infusion Rate using IMC.**

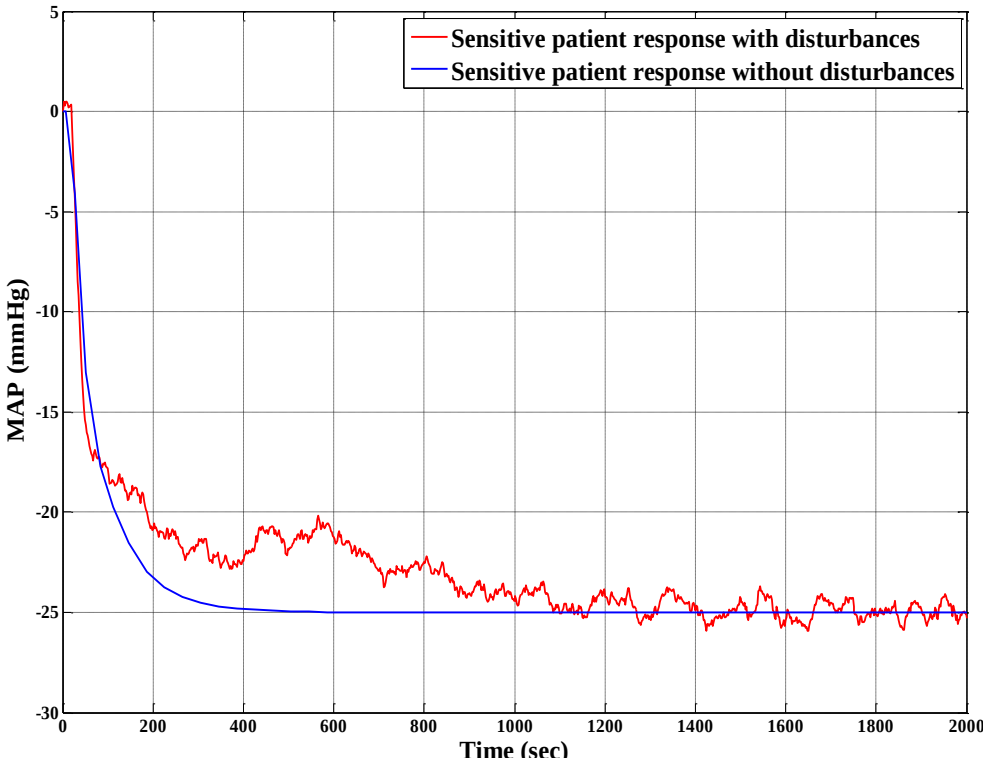



**Figure 4.10: Sensitive Patient Response with and without Disturbances using IMC.**

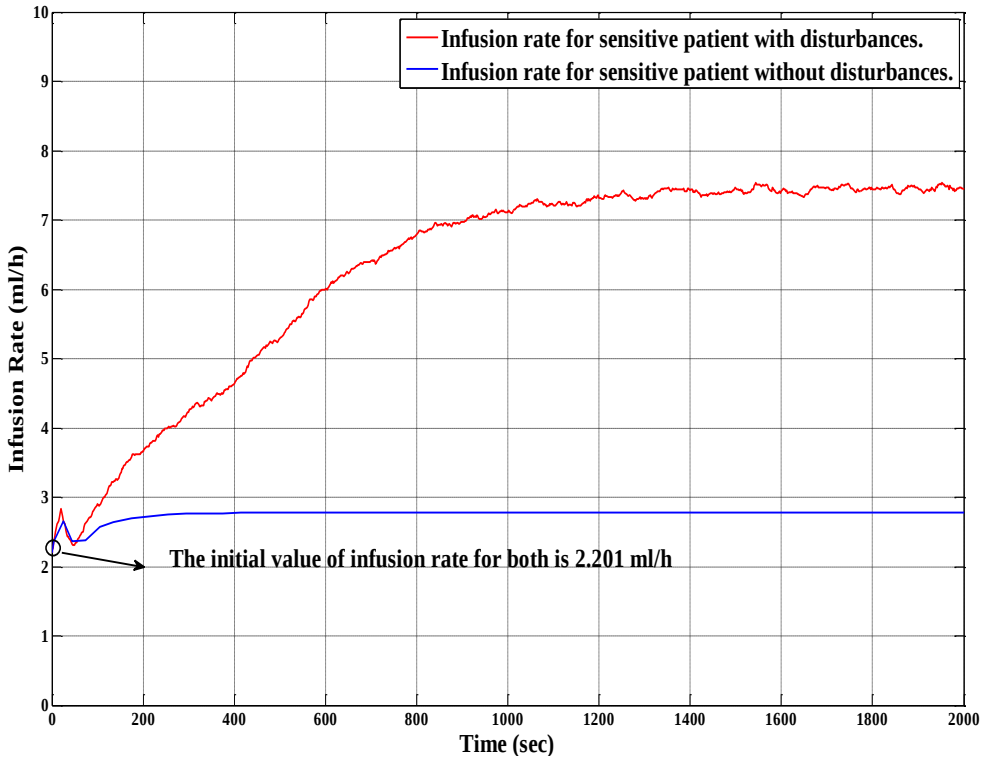



**Figure 4.11: Sensitive Patient Infusion Rate with and without Disturbances using IMC.**

### 4.3.2 PID Controllers

The three-term controller, PID, shown in **Figure** 4.12, has been widely used in the field of process control because of its simplicity and robustness. In conventional PID control, once the well-tuned PID gains are obtained, the controller usually exhibits good performance. However, when the dynamic characteristics of the system are time dependent or the operating conditions of the system vary, it is necessary to retune the PID parameters again. The manual tuning of PID controllers, which requires optimization of the parameters, is a time-consuming task. To deal with this difficulty, much effort has been invested in developing systematic tuning methods. Many of these methods depend on knowledge of the plant model. Some of these tuning methods are described in [83, 84].

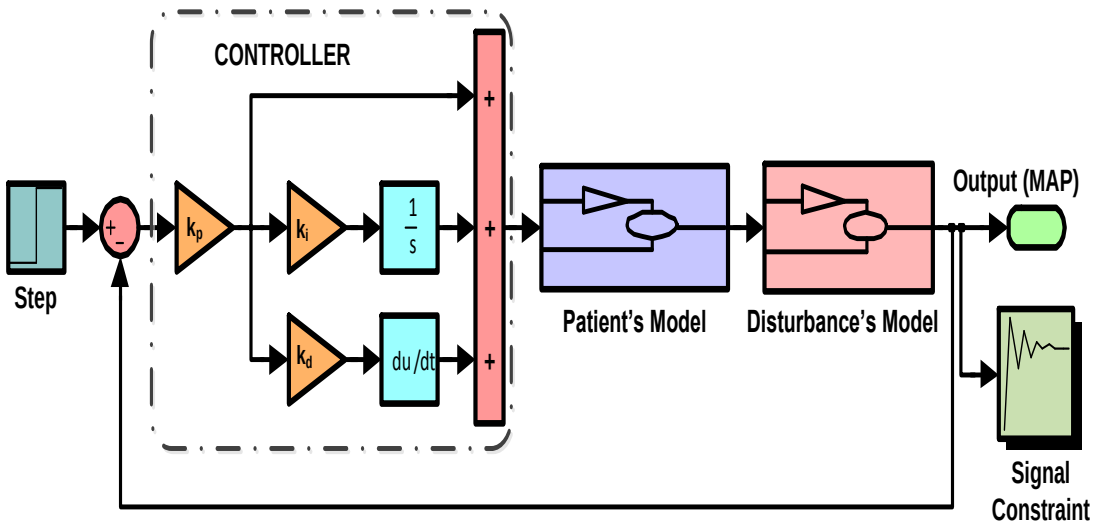



**Figure 4.12: Block Diagram of PID Controller with (GAs) Optimisation Technique.**

In this part, the GAs optimisation technique as one of the SROT methods has been implemented to obtain the optimal values of PID controller

parameters, $K_p$, $K_i$, and $K_d$. The optimisation results achieved satisfy the performance criteria and achieve the desired level of MAP (-30 and -25 mmHg) with optimal values of infusion rate, with and without disturbance as shown in **Table** 4-6, **Table** 4-7, **Table** 4-8 and **Table** 4-9 respectively.

**Table 4-6: PID Controller's Gain with Disturbances and Setpoint -30 mmHg.**

| Patient's type | Controller's Parameters | | | SNP (ml/h) | MAP (mmHg) |
|---|---|---|---|---|---|
| | $K_p$ | $K_i$ | $K_d$ | | |
| Sensitive | - 0.0898 | 0.0291 | 0.4592 | 7.984 | - 30.38 |
| Nominal | - 0.3167 | 0.0347 | 0.4919 | 72.12 | - 30.19 |
| Insensitive | - 1.1939 | 0.0244 | 1.714 | 289.1 | - 30.15 |

**Table 4-7: PID Controller's Gain without Disturbances and Setpoint -30 mmHg.**

| Patient's type | Controller's Parameters | | | SNP (ml/h) | MAP (mmHg) |
|---|---|---|---|---|---|
| | $K_p$ | $K_i$ | $K_d$ | | |
| Sensitive | 0.001 | - 0.6084 | 1.1129 | 3.333 | - 30 |
| Nominal | - 0.3188 | 0.0151 | -0.174 | 30.01 | - 30 |
| Insensitive | - 0.1852 | 0.0594 | - 0.1992 | 120.4 | - 30 |

The system has been tested using PID controller with and without disturbances and with different types of patient's sensitivities to SNP in order to decreases MAP by 30 mmHg. The simulation results of the patient's responses to the drug and the drug infusion rates are presented in **Table** 4-6 and **Table** 4-7. From these results we have observed that the drug infusion rates are more than 40% smaller in the absence of disturbances.

**Figure** 4.13, **Figure** 4.15 and **Figure** 4.17, show the simulation results of the system for sensitive, nominal and insensitive patient's responses to SNP, respectively. **Figure** 4.14, **Figure** 4.16 and **Figure** 4.18

display the infusion rates of SNP for each patient from these results we have observed that the initial infusion rate is different from patient to patient. The quantities of the initial drug's infusion rate are 2.694 ml/h for sensitive patient, 9.501 ml/h for nominal patient and 35.82 ml/h for insensitive patient.

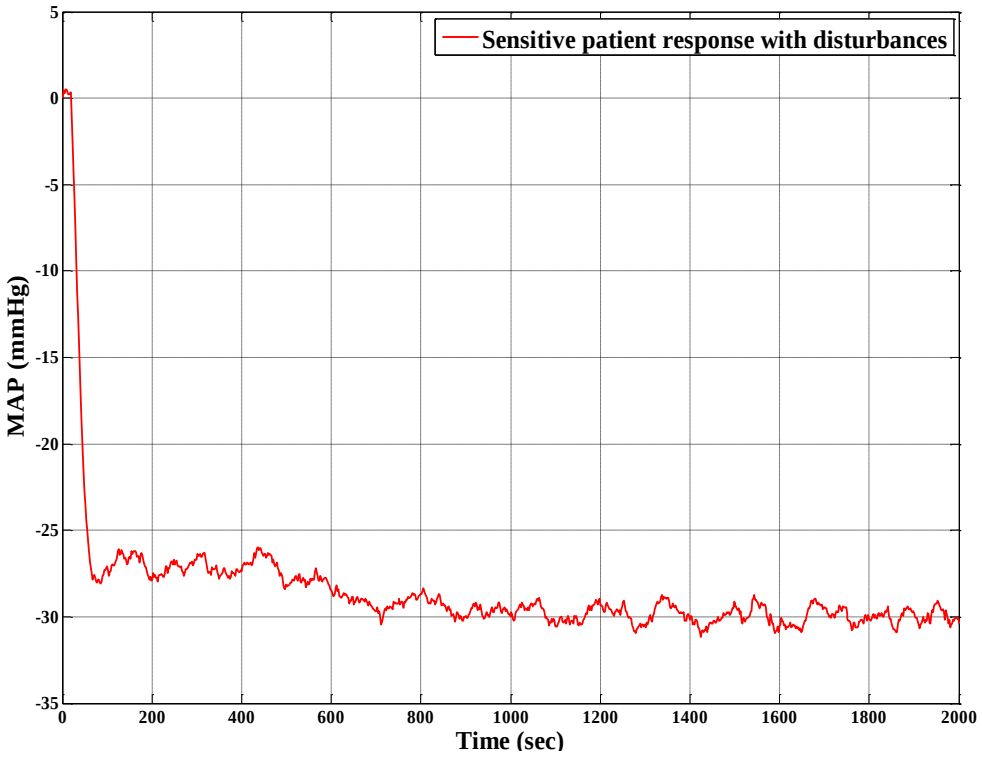



**Figure 4.13: Sensitive patient's response using PID.**

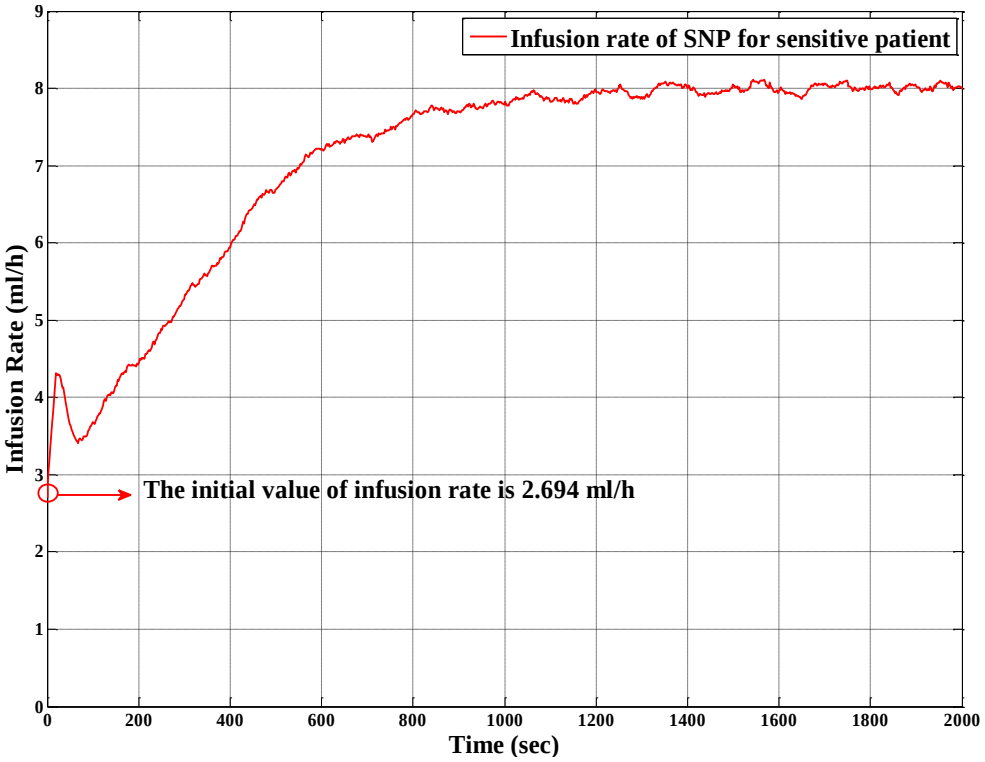



**Figure 4.14: Sensitive Patient's Infusion Rate using PID.**

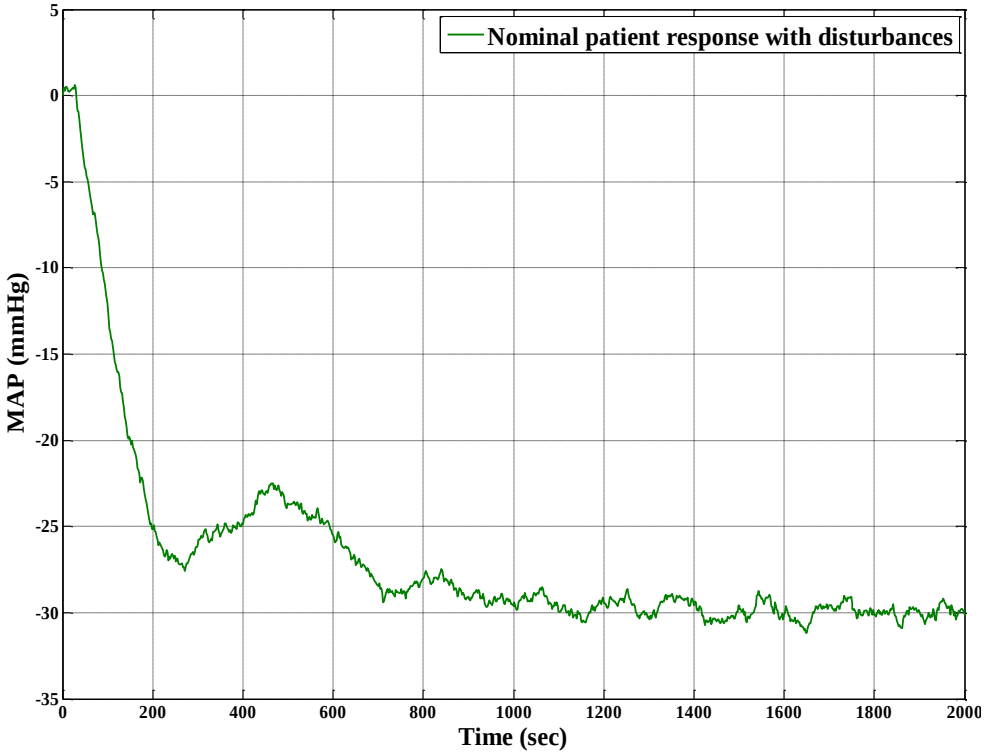



**Figure 4.15: Nominal Patient's Response using PID.**

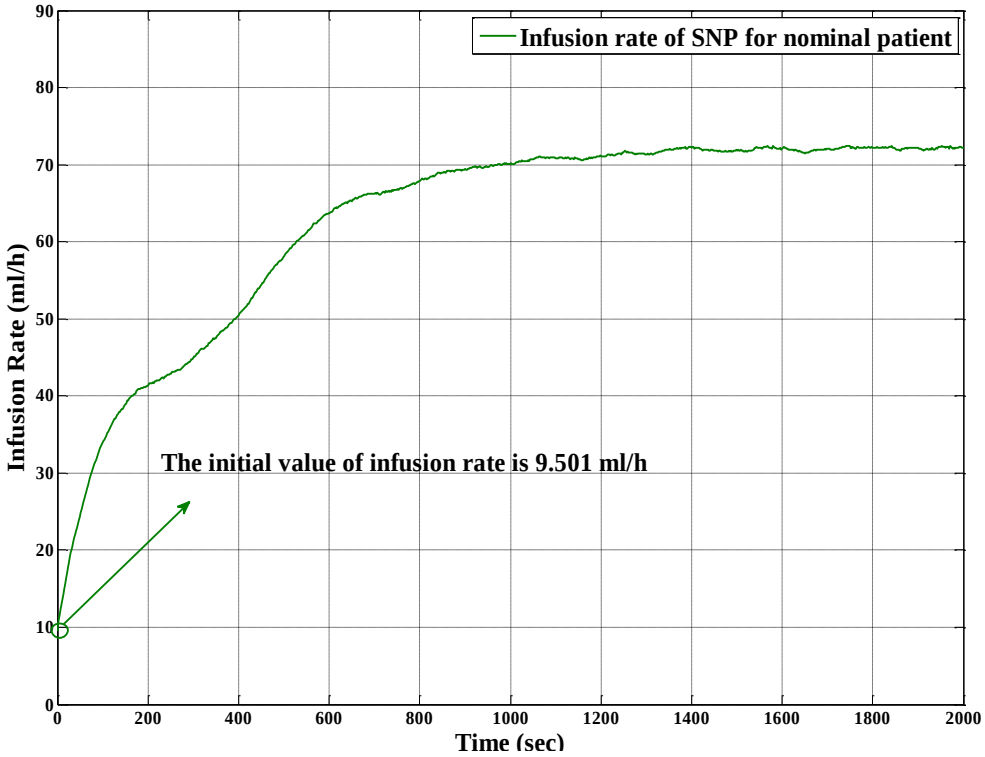



**Figure 4.16: Nominal Patient's Infusion Rate using PID.**

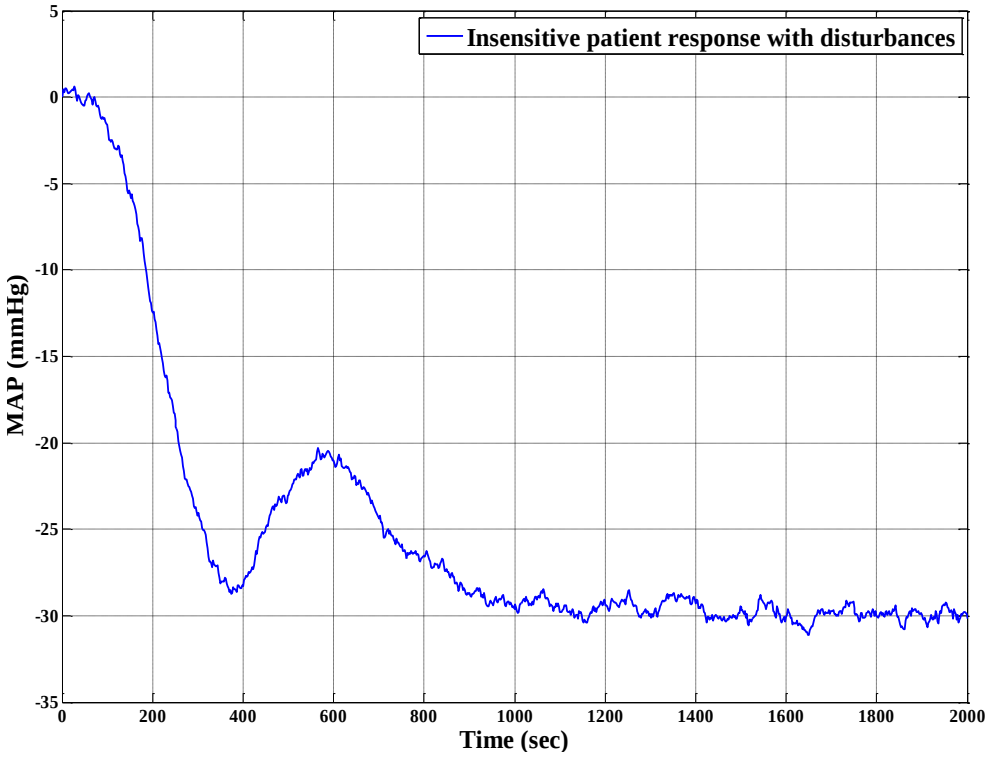



**Figure 4.17: Insensitive Patient's Response using PID.**

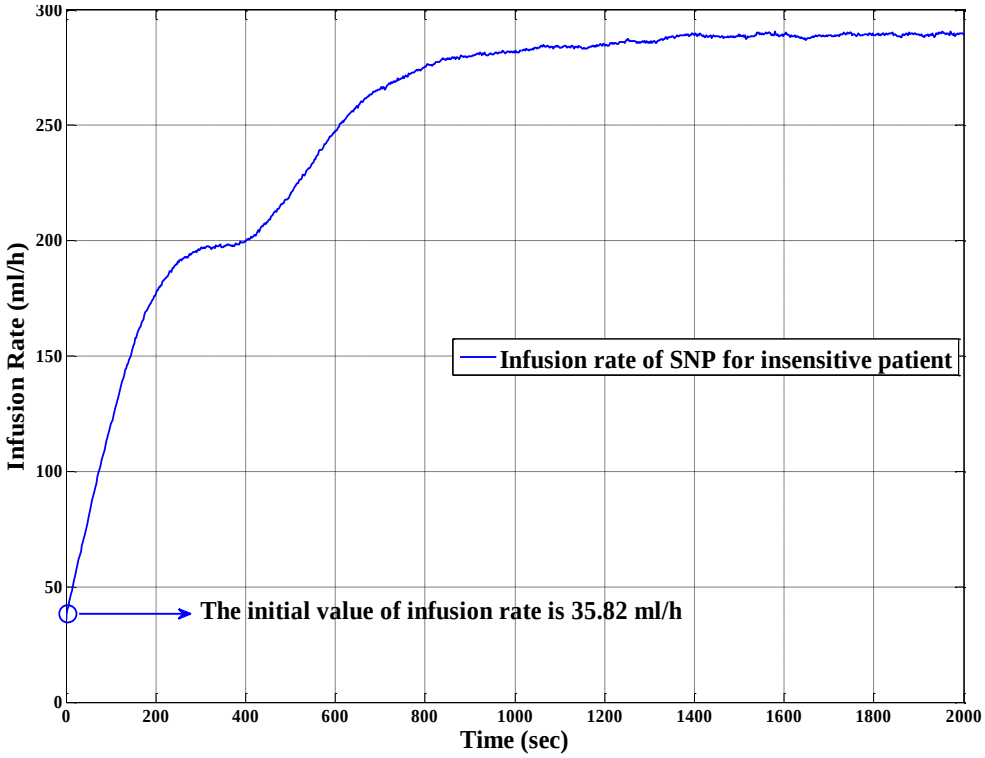



**Figure 4.18: Insensitive Patient's Infusion Rate using PID.**

**Table 4-8: PID Controller's Gain with Disturbances and Setpoint -25 mmHg.**

| Patient's type | Parameters | | | SNP (ml/h) | MAP (mmHg) |
|---|---|---|---|---|---|
| | $K_p$ | $K_i$ | $K_d$ | | |
| Sensitive | - 0.0898 | 0.0291 | 0.4592 | 7.427 | - 25.38 |
| Nominal | - 0.3167 | 0.0347 | 0.4919 | 67.11 | - 25.18 |
| Insensitive | - 1.1939 | 0.0244 | 1.714 | 269 | - 25.14 |

**Table 4-9: PID Controller's Gain without Disturbances and Setpoint -25 mmHg.**

| Patient's type | Parameters | | | SNP (ml/h) | MAP (mmHg) |
|---|---|---|---|---|---|
| | $K_p$ | $K_i$ | $K_d$ | | |
| Sensitive | 0.001 | - 0.6084 | 1.1129 | 2.778 | - 25 |
| Nominal | - 0.3188 | 0.0151 | - 0.174 | 25.01 | - 25 |
| Insensitive | - 0.1852 | 0.0594 | - 0.1992 | 100.3 | - 25 |

**Table** 4-8 and **Table** 4-9 illustrate the effect of the disturbances on the values of drug infusion rates when the desired level of MAP is -25 mmHg. For example the infusion rate for sensitive patient in the presence of disturbances is 7.427 ml/h and without disturbances is 2.778 ml/h.

**Figure** 4.19 and **Figure** 4.20 below shows the simulation results for sensitive patient response and the infusion rates of SNP when the desired level of MAP is -25 mmHg. From **Figure** 4.20 we have observed that the initial infusion rate ~~in~~ with disturbances is 2.245 ml/h but without disturbances the initial infusion rate is zero.

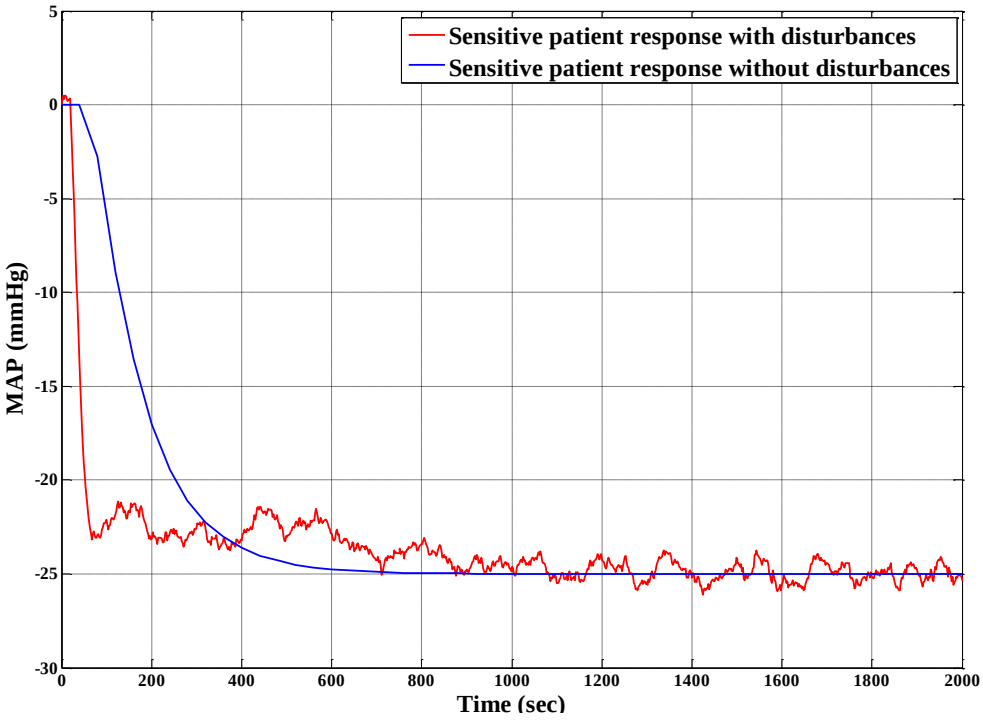



**Figure 4.19: Sensitive Patient Response with and without Disturbances using PID.**

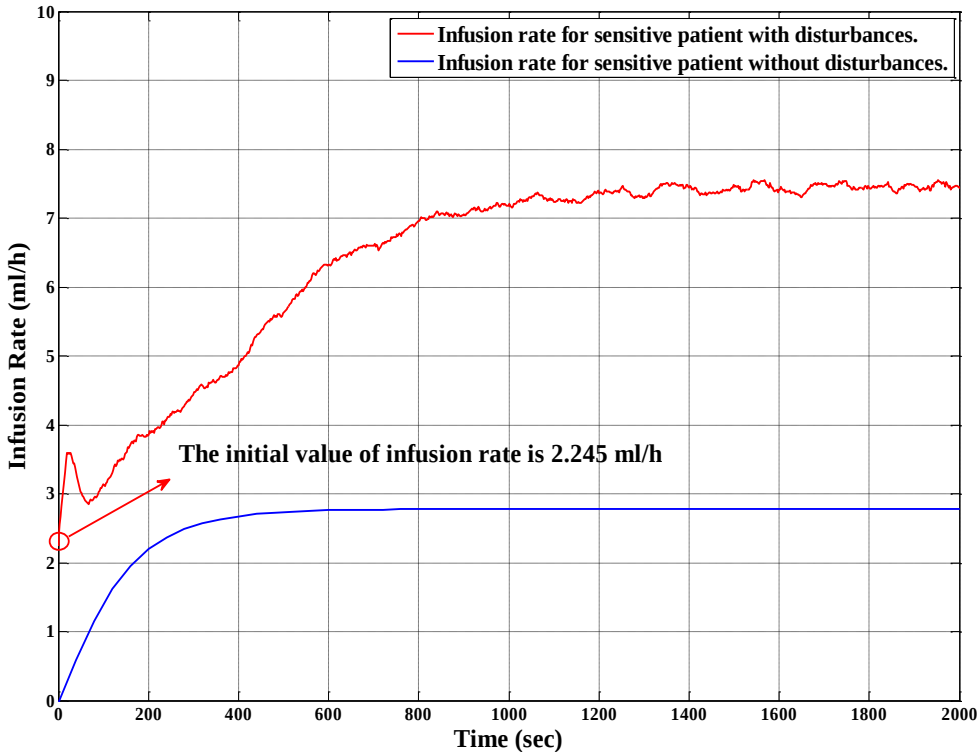



**Figure 4.20: Sensitive Patient Infusion Rate with and without Disturbances using PID.**

## 4.4 Comparison of Results

Both the IMC and the PID controllers were simulated using Matlab/Simulink and tested on three types of patient's model, the nominal, the sensitive and the insensitive. The optimal parameters of the controllers have been obtained using GAs optimisation. The patient's responses to the SNP drug were obtained in the presence of disturbances. The patient's model parameters are shown in **Table** 4-1.

**Figure** 4.21, **Figure** 4.22, **Figure** 4.23 and **Figure** 4.24 shows the simulation results of the nominal, sensitive and insensitive patient's responses to a step decrease of -30 mmHg in the SNP drug infusion rate with the PID and IMC controller respectively.

**Table** 4-10, **Table** 4-11 and **Table** 4-12 have displayed the time it takes the responses to reach -30 mmHg (settling time), (overshoot) and (Undershoot) for both controllers.

**Table 4-10: Performances of the Controllers for Sensitive Patient Model.**

| Parameters | PID | IMC |
|---|---|---|
| Setting Time (s) | 697 | 939 |
| Overshoot (mmHg) | 0 | 0 |
| Undershoot (mmHg) | 0.498 | 0.597 |

**Table 4-11: Performances of the Controllers for Nominal Patient Model.**

| Parameters | PID | IMC |
|---|---|---|
| Setting Time (s) | 1007 | 709 |
| Overshoot (mmHg) | 0 | 0 |
| Undershoot (mmHg) | 0.597 | 0.597 |

**Table 4-12: Performance of the Controllers for Insensitive Patient Model.**

| Parameters | PID | IMC |
|---|---|---|
| Setting Time (s) | 1123 | 1123 |
| Overshoot (mmHg) | 0 | 0 |
| Undershoot (mmHg) | 0.597 | 0.597 |

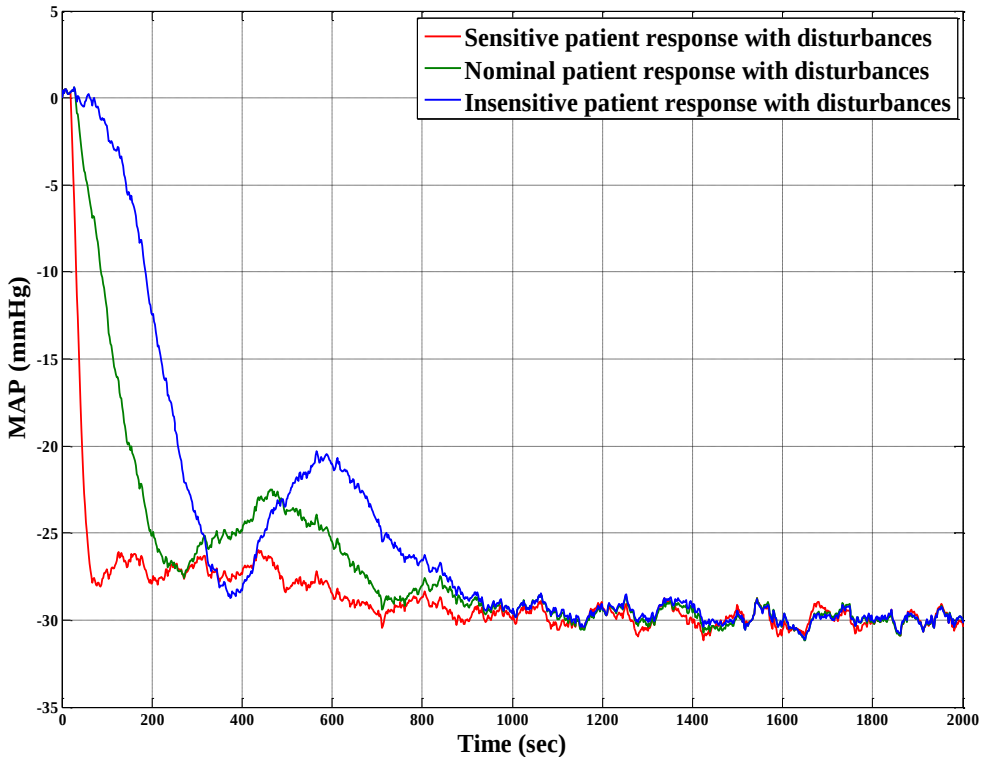



**Figure 4.21: Patient's responses using PID.**

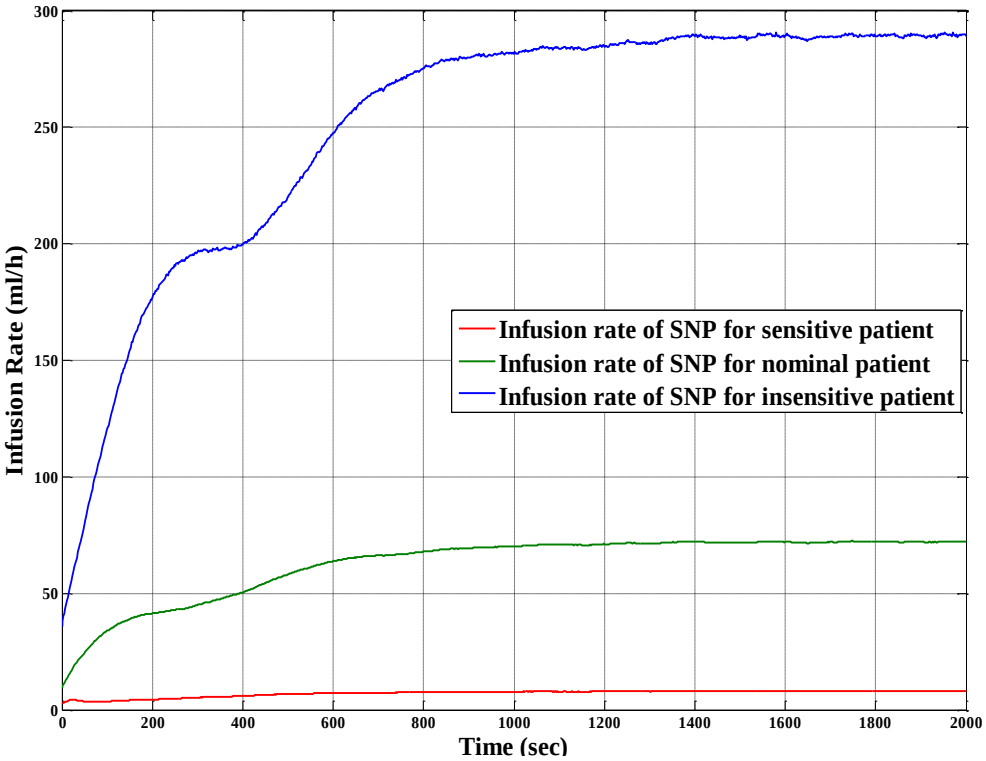



**Figure 4.22: Infusion Rates of SNP for Patients using PID.**

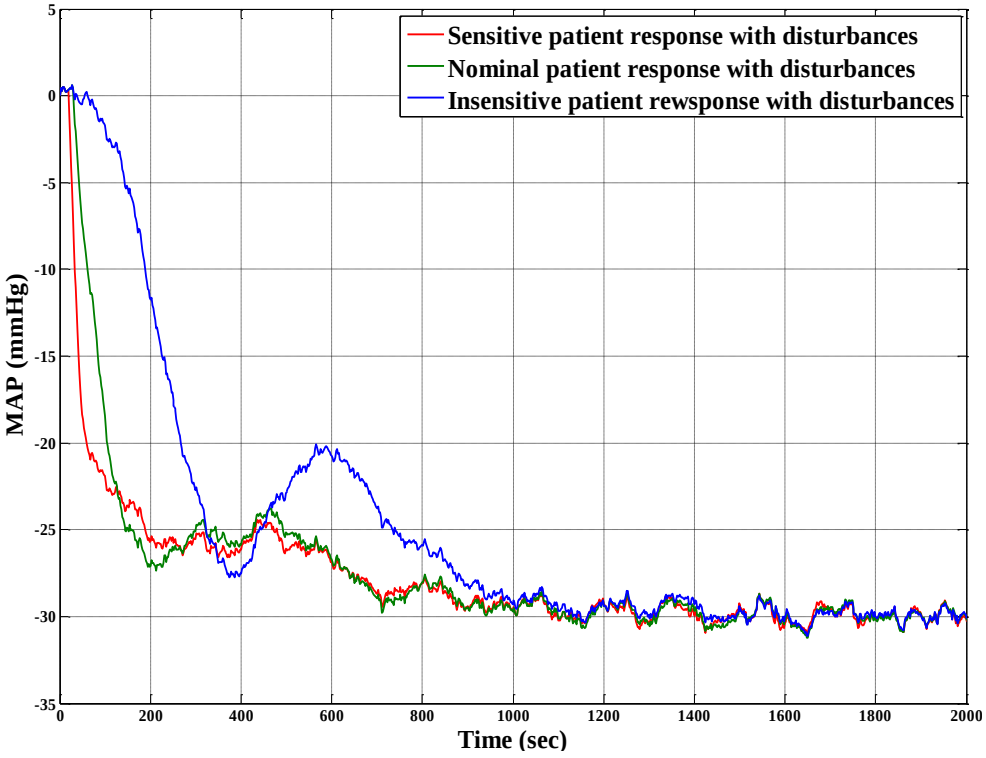



**Figure 4.23: Patient's Responses using IMC.**

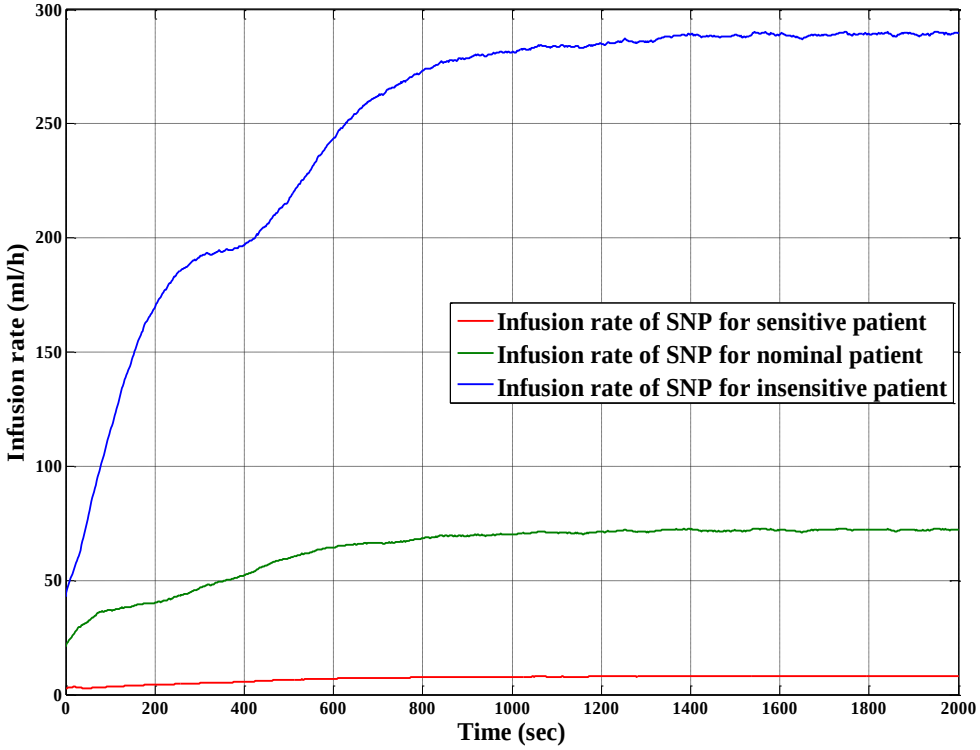



**Figure 4.24: Infusion Rates of SNP for Patients using IMC.**

These results demonstrate that the performance criteria are satisfied with both the PID controller and IMC controller. However, the settling time for the PID controller for sensitive patient's responses is shorter than with the IMC controller, the difference in settling time is around 242 s. The overshoot is zero with both controllers for the three types of patient. The IMC controller has achieved a shorter settling time than PID controller in nominal patient and the settling time is the same in insensitive patient. Both controllers have undershoot with little change, in sensitive patient. In nominal and insensitive types of patient the PID controller has a smaller value of undershoot. Also, in nominal and insensitive types of patient, both controllers have the same value of undershoot.

**Figure** 4.25, **Figure** 4.26 and **Figure** 4.27 depicts the performance of the PID and IMC control. Both have achieved the performance criteria which were specified in section 4.3. From **Figure** 4.28, **Figure** 4.29 and **Figure** 4.30 we observed that for the sensitive, nominal and insensitive patient the infusion rate of SNP achieved with PID control is more or less the same as with IMC as presented in **Table** 4-13 and **Table** 4-14. The maximum value of the infusion rate does not exceed 300 ml/h even for the "insensitive patient" as reported by Auer and Rodler [44]. As expected, the infusion rate for the sensitive patient is low, around 8 (ml/h), since this patient's model has zero recirculation factors. In nominal and insensitive patients, the PID controller has a smaller initial infusion rate than IMC controller**.**

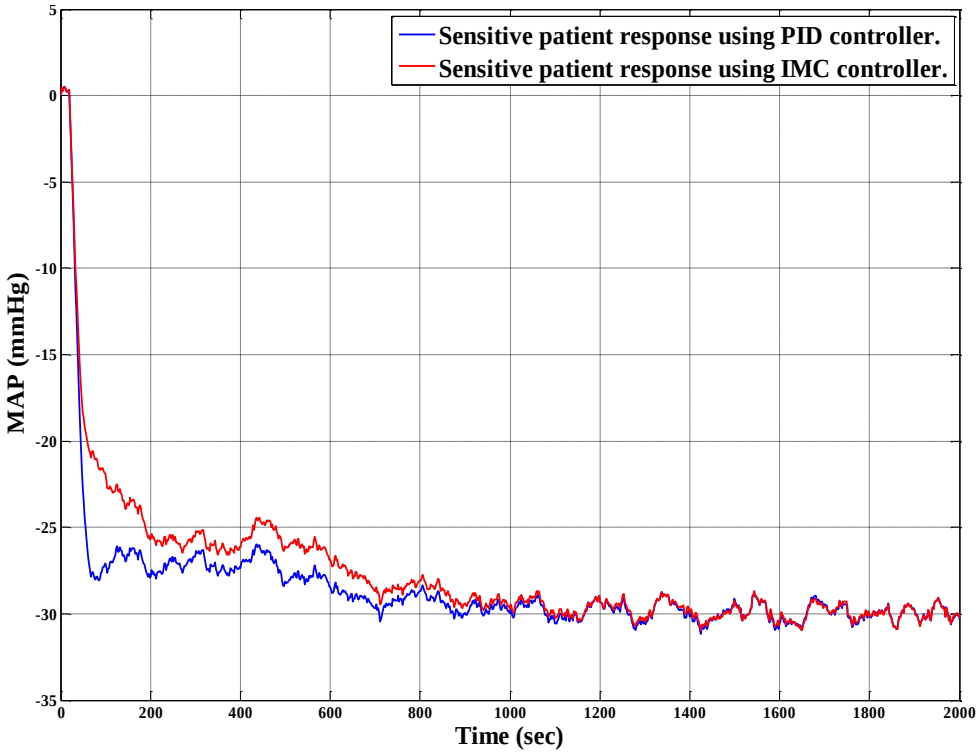



**Figure 4.25: Sensitive Patient Response using PID and IMC.**

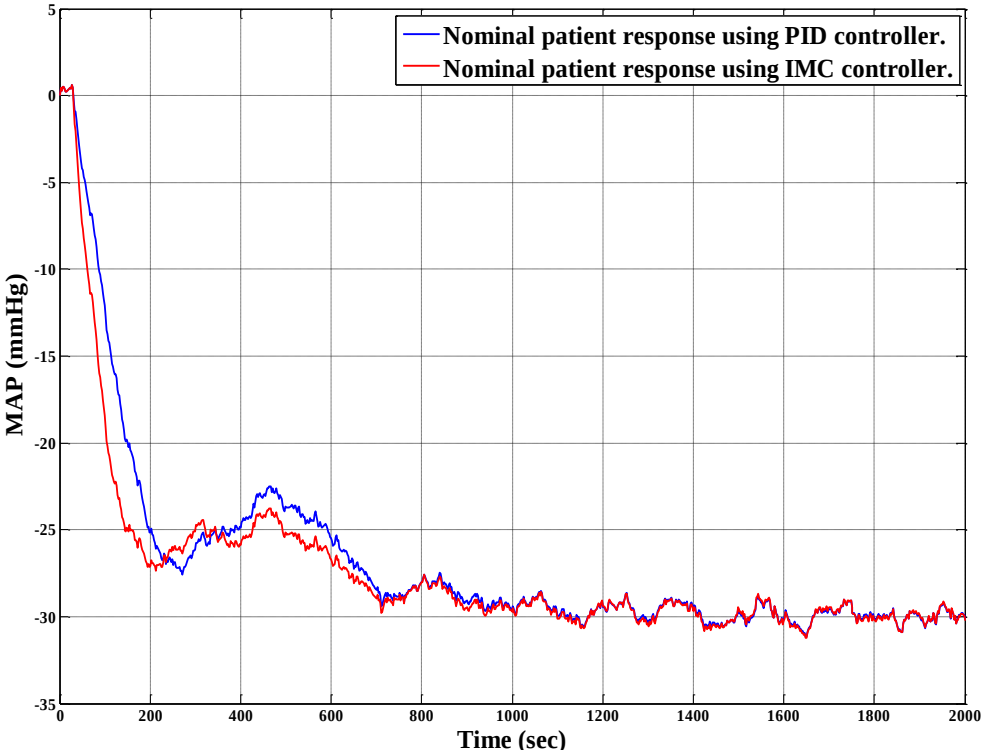



**Figure 4.26: Nominal Patient Response using PID and IMC.**

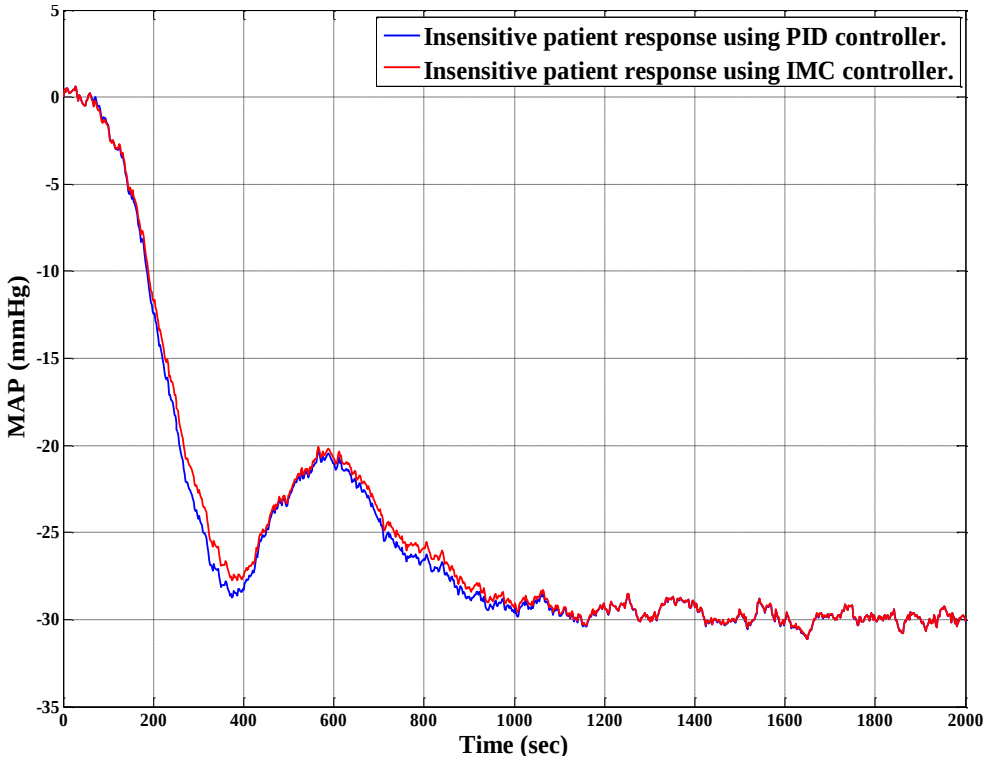



**Figure 4.27: Insensitive Patient Response using PID and IMC.**

**Table 4-13: SNP Infusion Rates for Patients using PID.**

| Patient's type | Final infusion rate (ml/h) | Initial infusion rate (ml/h) |
|---|---|---|
| Sensitive | 7.984 | 2.694 |
| Nominal | 72.12 | 9.501 |
| Insensitive | 289.1 | 35.82 |

**Table 4-14: SNP Infusion Rates for Patients using IMC Controller.**

| Patient's type | Final infusion rate (ml/h) | Initial infusion rate (ml/h) |
|---|---|---|
| Sensitive | 7.994 | 2.641 |
| Nominal | 72.08 | 20.88 |
| Insensitive | 289.3 | 42.98 |

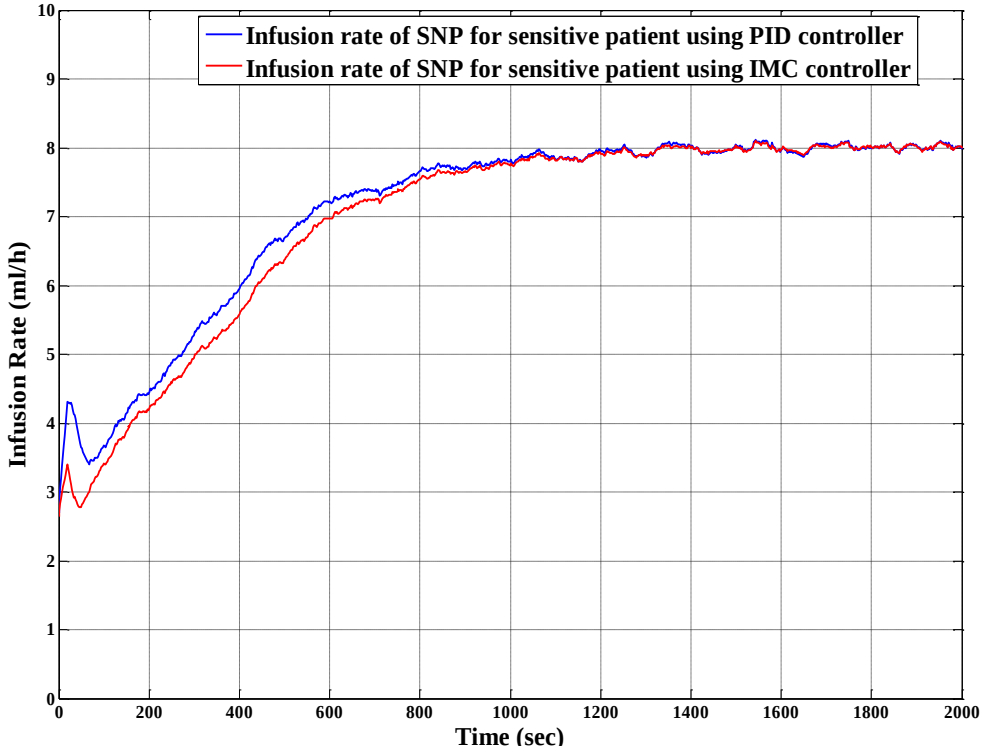



**Figure 4.28: SNP's Infusion Rate for Sensitive Patient using PID and IMC.**

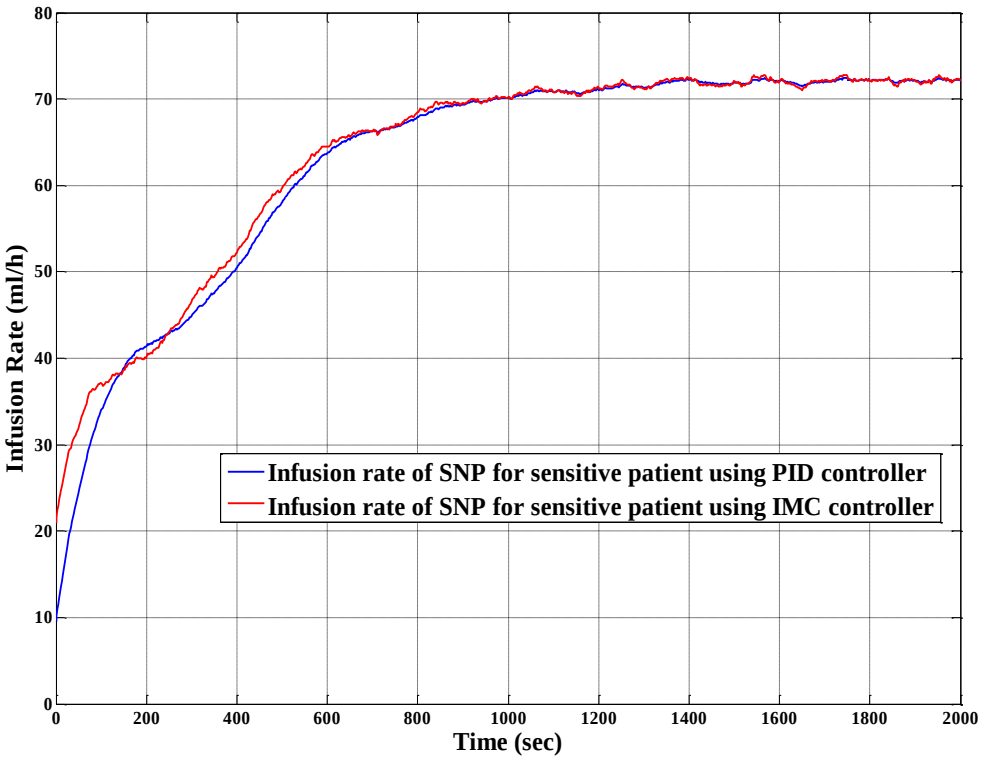



**Figure 4.29: SNP's Infusion Rate for Nominal Patient using PID and IMC.**

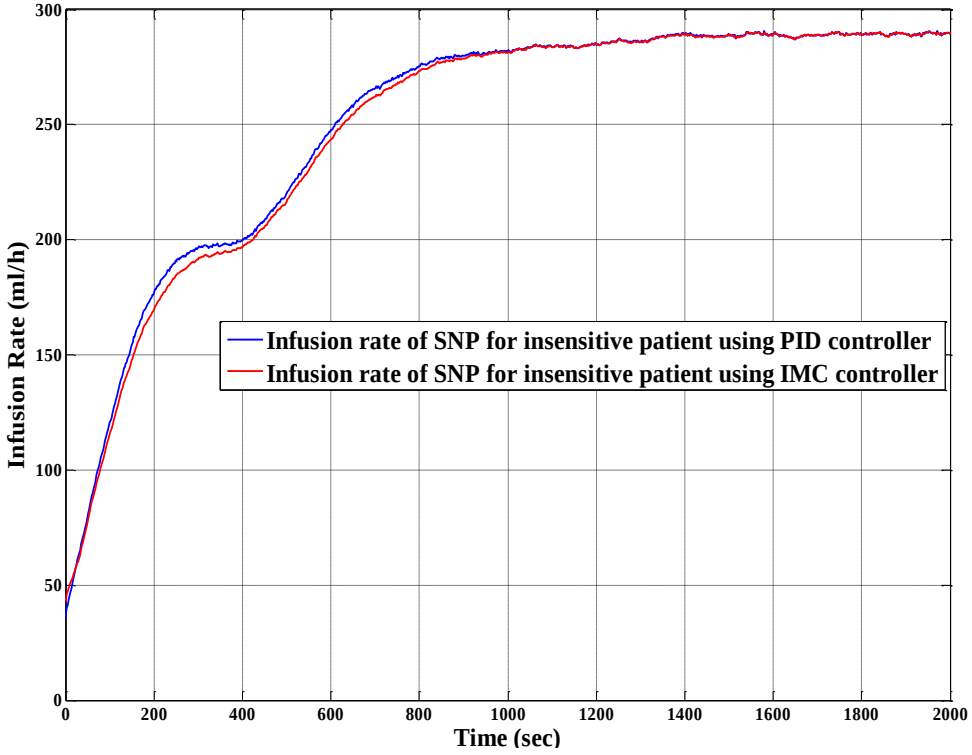



**Figure 4.30: SNP's Infusion Rate for Insensitive Patient using PID and IMC.**

## 4.5 Summary

The abnormal blood pressure is one of the most common complications which have been observed in postoperative patients. The infusion of the drugs is used to maintain the blood pressure at the desired level and its effect on the biological system presents a real problem in postoperative patients. The implementation of automatic control drug delivery system has the potential to improve patient care and reduce human error. This chapter has presented a comparison of performance between IMC and PID control of MAP for a single drug. The parameters of these controllers have been optimised using GAs optimisation technique. The resulting controllers are tested on different sensitivity types of patients' response to SNP, for the desired MAP drop level.

In **Chapter** 5, the MRAC control system has been designed and implemented to regulate MAP and CO using two drugs, SNP and DPM.

# Chapter 5.

## MRAC FOR MULTI-INPUT MULTI-OUTPUT (MIMO) PATIENT RESPONSE MODEL

### 5.1 Introduction

If blood pressure is controlled and oscillations in the hemodynamic variables are reduced, patients experience fewer complications after surgery. In clinical practice, this is usually achieved using manual drug delivery. Given that different patients have different sensitivity and reaction time to drugs, determining manually the right drug infusion rates may be difficult. This is a problem where automatic drug delivery can provide a solution, especially if it is designed to adapt to variations in the patient's model.

Various automatic control techniques have been used to control the hemodynamic variables. Many studies have focused on the infusion of a single drug to lower the patients' blood pressure and maintain it at the desired level using in particular the vasoactive drug sodium nitroprusside SNP [7, 47, 49, 83, 103-106] and [25]. In chapter four we have covered the MAP regulation using single drug, implementing two types of controller, PID and IMC and the results have been published [107]. Slate and Sheppard in 1982 have used a one-drug patient model and implemented a nonlinear digital PID controller to regulate MAP [7]. In 2005, Zheng and Zhu developed a MMAC based on FC [106]. In 1991, Behbehain and Cross proposed an integrating self-tuning control strategy to maintain MAP using SNP [108]. In a

recent study Zhu et al. in 2008 presented an adaptive control algorithm for updating time delays and sensitivity of the hemodynamic model [109]. Poterlowicz et al. in 2007 and 2008 developed an optimal IMC system to regulate MAP with the SNP drug [47, 49].

Blood pressure is commonly controlled using more than one drug. Several studies have investigated the automation of multiple drug-deliveries. Yu et al. in 1990 developed a computer model to simulate the hemodynamic variables responses to DPM and SNP in a failing heart [10]. They simulated the circulatory system with a nonlinear electrical analog model with baroreflex feedback. In 1999, Achuthan et al. used the computer model developed in 1990 by Yu et al. to test an indirect adaptive algorithm based on parameter identification and linear quadratic regulation [11]. An adaptive algorithm to control MAP and CO in anesthetized dogs with infusion of SNP and DPM has been implemented by Voss et al. in 1987 [12]. Yu et al. in 1992 proposed an algorithm that utilized six model predictive controllers to regulate MAP and CO with SNP and DPM. They carried out tests on laboratory animals that were altered to exhibit symptoms of congestive heart failure [13]. Due to the variations in plant parameters and time delay elements. Ozecelik et al. in 1999 have developed and implemented the robust DMRAC to regulate MAP and CO using SNP and DPM [71]. Several experiments have been done on animal using multi-drug administration system, Koivo et al. in 1978, 1980 and 1981 [14-16]., Stern et al. in 1981 [17] and in 1984 by Kaufman et al. [18].

In this chapter we have used a two-input, two-output patient model with matrix elements represented by first-order transfer functions with time delays to investigate the performance of a MRAC system. The controller parameters have been adapted using the diagonal (6×6) weighting matrices discussed in [63]. Matlab Simulink Toolbox was used to design and simulate the proposed control system.

## 5.2 Patients' Model Description

The objective of the control system is to decrease the patient's MAP and increase CO to the desired values by tracking the reference signals. In this chapter we have adapted the patients' hemodynamic model which first introduced by Ozcelik et al. [71]. This model has been defined by the linear small-signal first-order transfer function matrix as given in **Equation** (5.1). The drugs used to control the variables CO and MAP are DPM and SNP. DPM increases both CO and MAP while SNP increases CO and decreases MAP. The drug infusion rates are measured in (µg/min.kg), CO is measured in (ml/min.kg) and MAP is measured in millimetres of mercury (mmHg).

$$\begin{bmatrix} \Delta \mathrm{CO}(s) \\ \Delta \mathrm{MAP}(s) \end{bmatrix} = \begin{bmatrix} \dfrac{\mathrm{K}_{11}\mathrm{e}^{-\mathrm{T}_{11}s}}{\tau_{11}s+1} & \dfrac{\mathrm{K}_{12}\mathrm{e}^{-\mathrm{T}_{12}s}}{\tau_{12}s+1} \\ \dfrac{\mathrm{K}_{21}\mathrm{e}^{-\mathrm{T}_{21}s}}{\tau_{21}s+1} & \dfrac{\mathrm{K}_{22}\mathrm{e}^{-\mathrm{T}_{22}s}}{\tau_{22}s+1} \end{bmatrix} \begin{bmatrix} \Delta \mathrm{DPM}(s) \\ \Delta \mathrm{SNP}(s) \end{bmatrix} \tag{5.1}$$

where, the $K_{ij}$ is referring to the model gains. The $T_{ij}$ represent the time delays between inputs and the system responses measured in units of (s). $\tau_{ij}$, represent the system time constants in units of (s).

During clinical evaluations of the patient model, it was observed that disturbances could have an effect on the patient's hemodynamic states, which could lead to an increase or decrease in blood pressure [7]. Therefore **Equation** (5.1) was modified to include the disturbance terms $D_1$ and $D_2$ as shown in **Equation** (5.2) below, where $D_1$ and $D_2$ are the disturbances in CO and MAP.

$$\begin{bmatrix} \Delta CO(s) \\ \Delta MAP(s) \end{bmatrix} = \begin{bmatrix} \frac{K_{11}e^{-T_{11}s}}{\tau_{11}s+1} & \frac{K_{12}e^{-T_{12}s}}{\tau_{12}s+1} \\ \frac{K_{21}e^{-T_{21}s}}{\tau_{21}s+1} & \frac{K_{22}e^{-T_{22}s}}{\tau_{22}s+1} \end{bmatrix} \begin{bmatrix} \Delta DPM(s) \\ \Delta SNP(s) \end{bmatrix} + \begin{bmatrix} D_1 \\ D_2 \end{bmatrix} \tag{5.2}$$

and

$$CO = \frac{K_{11}e^{-T_{11}s}}{\tau_{11}s+1} \times DPM + \frac{K_{12}e^{-T_{12}s}}{\tau_{12}s+1} \times SNP + D_1 \tag{5.3}$$

$$MAP = \frac{K_{21}e^{-T_{21}s}}{\tau_{21}s+1} \times DPM + \frac{K_{22}e^{-T_{22}s}}{\tau_{22}s+1} \times SNP + D_2 \tag{5.4}$$

The patient SIMULINK model has been built from **Equations** (5.3) and (5.4), and the SIMULINK block diagram of the hemodynamic model is shown in **Figure** 5.1.

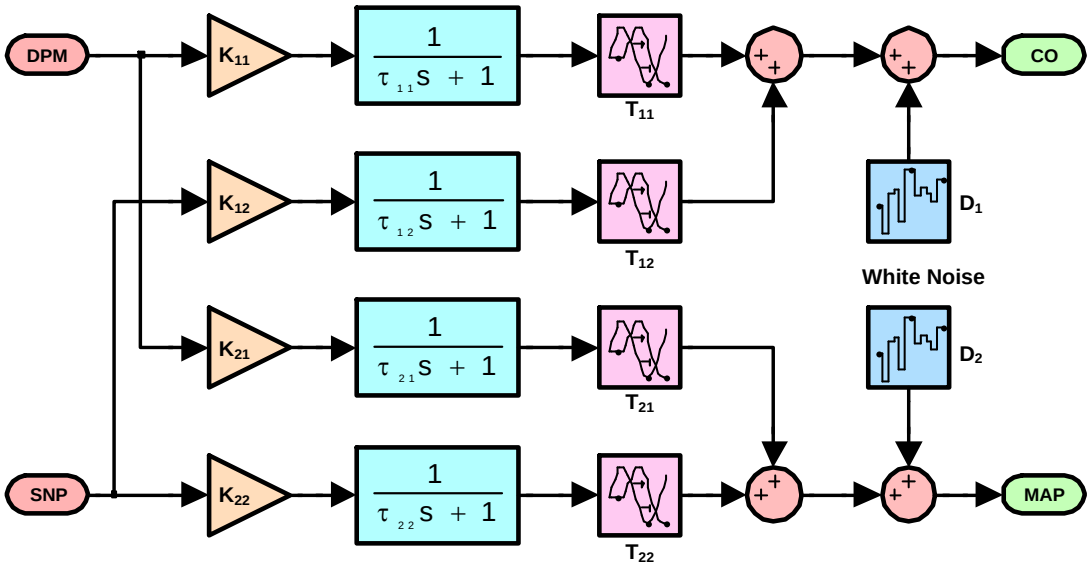



**Figure 5.1: Simulink Block Diagram of the Plant Model.**

The nominal values and range of the parameters in the patient model are given in **Table** 5-1.

The desired response is represented by the reference model transfer function of CO and MAP as shown in **Equation** (5.5) [63].

$$H(s) = \frac{y_{mi}(s)}{u_{mi}(s)} = \frac{1}{\tau_i s + 1} \tag{5.5}$$

where, $y_{m1}$ and $y_{m2}$ are the outputs of the first and second reference model respectively. $u_{m1}$ and $u_{m2}$ are the inputs of the first and second reference model respectively, $\tau_1$= 300 s. and $\tau_2$= 90 s. are the time constants of the reference models chosen to produce the desired speed of hemodynamic response. The constraints on normalized drug dosage are selected as follows: 0 ≤ DPM ≤ 6 mg\min.kg and 0 ≤ SNP ≤ 10 mg\min.kg.

**Table 5-1: Nominal Values and Range of the Parameters in the Patient Model.**

| parameters | Nominal | Ranges | Unit |
|---|---|---|---|
| $K_{11}$ | 5 | 1 to 12 | ml/$\mu$g |
| $\tau_{11}$ | 300 | 70 to 600 | s |
| $T_{11}$ | 60 | 15 to 60 | s |
| $K_{12}$ | 12 | -15 to 25 | ml/$\mu$g |
| $\tau_{12}$ | 150 | 70 to 600 | s |
| $T_{12}$ | 50 | 15 to 60 | s |
| $K_{21}$ | 3 | 0 to 9 | mmHg/$[\mu g / \min.kg]$ |
| $\tau_{21}$ | 40 | 30 to 60 | s |
| $T_{21}$ | 60 | 15 to 60 | s |
| $K_{22}$ | -15 | -13 to -50 | mmHg/$[\mu g / \min.kg]$ |
| $\tau_{22}$ | 40 | 30 to 60 | s |
| $T_{22}$ | 50 | 15 to 60 | s |

## 5.3 Model Reference Adaptive Control System

**Figure** 5.2 shows the diagram of the patient's model and MRAC system. The MATLAB function block is used to obtain the reference signal $u_m$ depending on the patient's case.

The control signal $u_p(t)$ which represents the drug infusion rate is formulated as a linear combination of the error feedback [$K_e(t)$ x e] and the two feed-forwards reference model output [$K_y(t)$ x $y_m$] and reference model input [$K_u(t)$ x $u_m$]. The adaptive control law combines the values of the tracking error e, the reference model output $y_m$ and the reference model input

$u_m$ with appropriate adaptive gains [$K_y$, $K_u$ and $K_e$] [110]. The adaptive control law is given by:

$$U_p(t) = K_y(t) \times y_m(t) + K_u(t) \times u_m(t) + K_e(t)\left[y_m(t) - y_p(t)\right] \quad (5.6)$$

$$U_p(t) = K_r(t) \times r(t) \quad (5.7)$$

$$K_r(t) = [K_e, \quad K_y, \quad K_u]$$

$$\therefore \; K_r(t) = K_p(t) + \hat{K}_i(t) \quad (5.8)$$

$$r(t) = \begin{bmatrix} e(t) \\ y_m(t) \\ u_m(t) \end{bmatrix} \quad (5.9)$$

where, $e(t) = y_m(t) - y_p(t)$

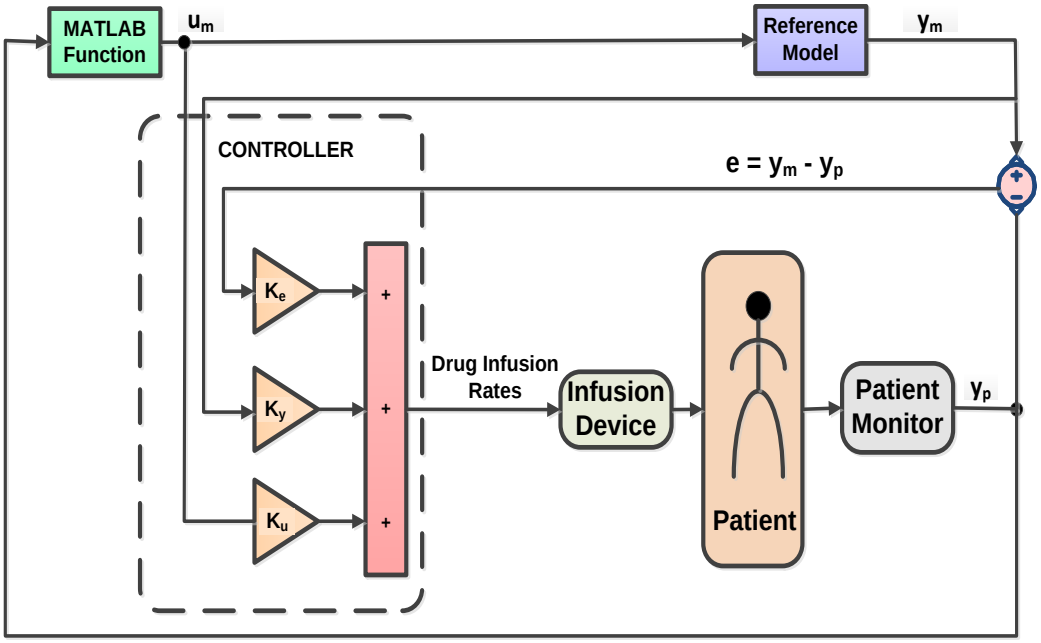



**Figure 5.2: General form of the patient's model with MRAC.**

The adaptive gain vector $K_r(t)$ in **Equation** (5.8) is obtained as a combination of integral and proportional gains as follows:

$$K_p(t) = e(t) \times r^T \times A \tag{5.10}$$

$$\hat{K}_i(t) = e(t) \times r^T \times B \tag{5.11}$$

where,

A and B are $n_r$ by $n_r$ (6 x 6) time invariant weighting matrices.

$$A = \begin{bmatrix} A_1 & 0 & 0 & 0 & 0 & 0 \\ 0 & A_2 & 0 & 0 & 0 & 0 \\ 0 & 0 & A_3 & 0 & 0 & 0 \\ 0 & 0 & 0 & A_4 & 0 & 0 \\ 0 & 0 & 0 & 0 & A_5 & 0 \\ 0 & 0 & 0 & 0 & 0 & A_6 \end{bmatrix} \quad B = \begin{bmatrix} B_1 & 0 & 0 & 0 & 0 & 0 \\ 0 & B_2 & 0 & 0 & 0 & 0 \\ 0 & 0 & B_3 & 0 & 0 & 0 \\ 0 & 0 & 0 & B_4 & 0 & 0 \\ 0 & 0 & 0 & 0 & B_5 & 0 \\ 0 & 0 & 0 & 0 & 0 & B_6 \end{bmatrix}$$

As the system has two inputs and two outputs we have designed two controllers, the function of the first controller is to control the infusion rate of the first drug DPM and the second controller to control the infusion rate of the second drug SNP. **Figure** 5.3 depicts the Simulink block diagram of the system. The Up1 and Up2 represented the outputs of both controllers respectfully as shown in **Equation** (5.12) and **Equation** (5.13).

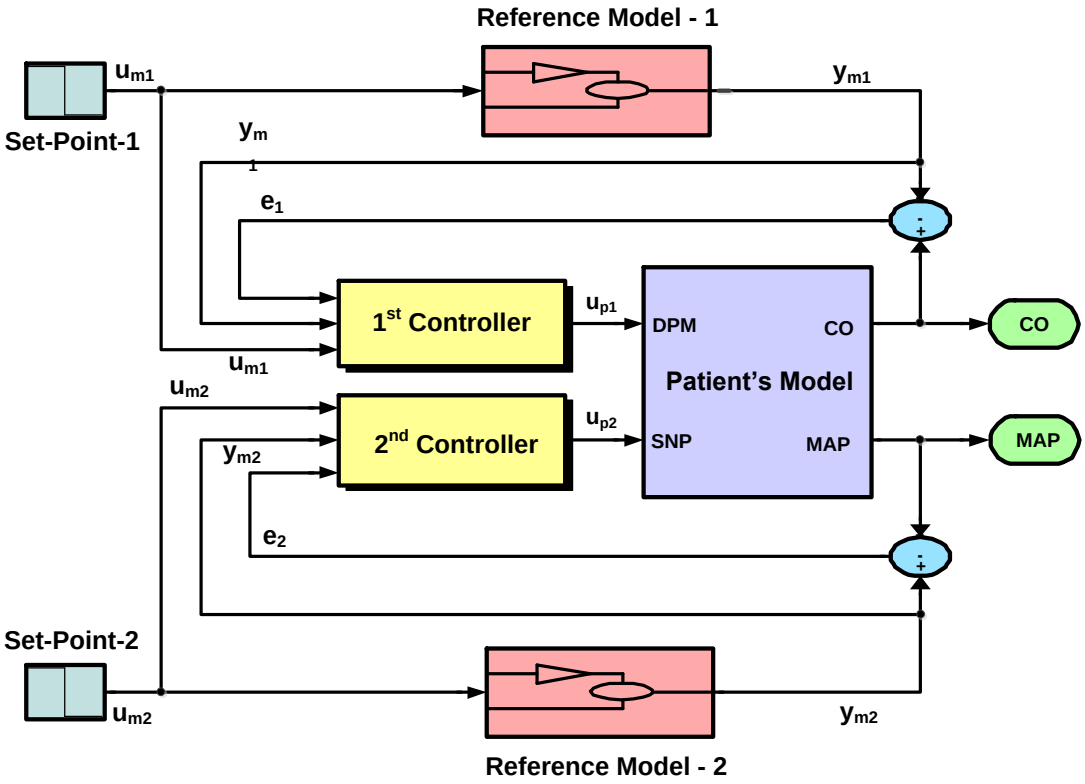



**Figure 5.3: Simulink Block Diagram of the Patient Model with the MRAC.**

$$U_{p1} = \left[K_{p1}(t) + \widehat{K_{i1}}(t)\right] r(t) \tag{5.12}$$

$$U_{p2} = \left[K_{p2}(t) + \widehat{K_{i2}}(t)\right] r(t) \tag{5.13}$$

### 5.3.1 Control Objectives

The performance of the MRAC is investigated by simulating two patients' situations where both MAP and CO are outside the normal values of 120 mmHg for MAP and 100 ml/min.kg for CO. The initial values of the patients' MAP and CO are chosen as 140 mmHg and 80 ml/min.kg respectively. The control objective is to decrease MAP down to 120 mmHg and increase CO up to 100 ml/min.kg.

**Table** 5-2 below presents the values of diagonal matrix which have been obtained and used to adapt the controllers.

**Table 5-2: The Values of A and B Diagonal.**

| $A_1$ | $A_2$ | $A_3$ | $A_4$ | $A_5$ | $A_6$ |
|---|---|---|---|---|---|
| $2x10^{-06}$ | $1.6x10^{-04}$ | $2.9x10^{-06}$ | $10^{-07}$ | $4.x10^{-10}$ | $10^{-04}$ |
| $B_1$ | $B_2$ | $B_3$ | $B_4$ | $B_5$ | $B_6$ |
| $10^{-05}$ | $2.8x10^{-08}$ | $1.1x10^{-06}$ | $10^{-06}$ | $10^{-08}$ | $10^{-10}$ |

Many simulation trials were conducted to find the best values of the above matrices that give MAP and CO responses within specifications. The performance was obtained using the values shown above.

## 5.4 Simulation Results

The proposed algorithm has been implemented, and tested through a set of experiments by considering decreasing MAP by 20 mmHg and increasing CO by 20 ml/min.kg.

**Table** 5-1 presents the lists of the nominal values and the range of the parameters of patient's model which were simulated using Matlab/Simulink as shown in **Figure** 5.3. The simulations were done for different patient's sensitivity. The MRAC has been implemented to compute the drugs infusion rates which are the inputs to the MIMO patient model.

Simulations were conducted for all the parameters values in the range to find by trial and error the best weighting matrices A and B. The proportional and integral gains were then calculated from **Equation** (5.10) and **Equation** (5.11) using these weighting matrices.

In order to compare the performance of our MRAC with previous research work as in [63], the comparisons have been done without the presence of disturbances on the patient's model. The simulations were also carried out with $K_{22}$ in the range -15, -20, and -50 ($mmHg/[\mu g/min.kg]$). These are shown in the following figures, **Figure** 5.4, **Figure** 5.5, **Figure** 5.6, **Figure** 5.7, **Figure** 5.8 and **Figure** 5.9 and data is presented in **Table** 5-3.

**Table 5-3: Comparisons between MRAC and Non-Adaptive PID.**

| Hemodynamic Variables | $K_{22}$ | Performance Measures | Results using MRAC | Results using non-adaptive PID | Results of [63] using MRAC |
|---|---|---|---|---|---|
| MAP | -20 | Settling Time (s) | 544 | 293 | 1320 |
| | | Overshoot (mmHg) | zero | zero | 4 |
| | -50 | Settling Time (s) | 506 | 345 | 660 |
| | | Overshoot (mmHg) | zero | 0.71 | 1.75 |
| CO | -20 | Settling Time (s) | 1232 | 887 | 1440 |
| | | Overshoot (ml/min.kg) | zero | Zero | Little |
| | -50 | Settling Time (s) | 1822 | 1100 | 1380 |
| | | Overshoot (ml/min.kg) | zero | 1.73 | Little |

We observe that the overshoot of both MAP and CO is zero. However, in [63] the MAP overshoots by 20% when $K_{22}$ = -20. The MRAC showed some improvements when $K_{22}$ = -20. **Figure** 5.8 and **Figure** 5.9 shows the simulation results of patient model and reference model responses when $K_{22}$ = -50. In this case the simulation needs more than 7500 s to illustrate the full system response. From this we observed that in this patient's case the system response needs more time to reach the desired level of MAP and CO as compared with other cases, also **Figure** 5.8 shows that system response of MAP has slight oscillation within 0.4 mmHg. The **Figure** 5.10 has displays these oscillations more clearly.

**Table 5-4: System Responses and Drugs Infusion Rates.**

| **Patient's case ($K_{22}$)** *"mmHg/[µg/min.kg]* | **MAP** *"mmHg"* | **CO** *"ml/min.kg"* | **SNP** *"µg/min.kg"* | **DPM** *"µg/min.kg"* |
|---|---|---|---|---|
| -15 | -15 | 15 | 1.081 | 0.4053 |
| -20 | -15 | 15 | 0.8824 | 0.8821 |
| -50 | -15 | 15 | 0.419 | 1.986 |
| -15 | -20 | 20 | 1.441 | 0.5405 |
| -20 | -20 | 20 | 1.176 | 1.176 |
| -50 | -20 | 20 | 0.5594 | 2.657 |

**Table** 5-4 presents the simulation results of the system responses and the optimal infusion rates of SNP and DPM for different patient's case with different desired level of MAP and CO.

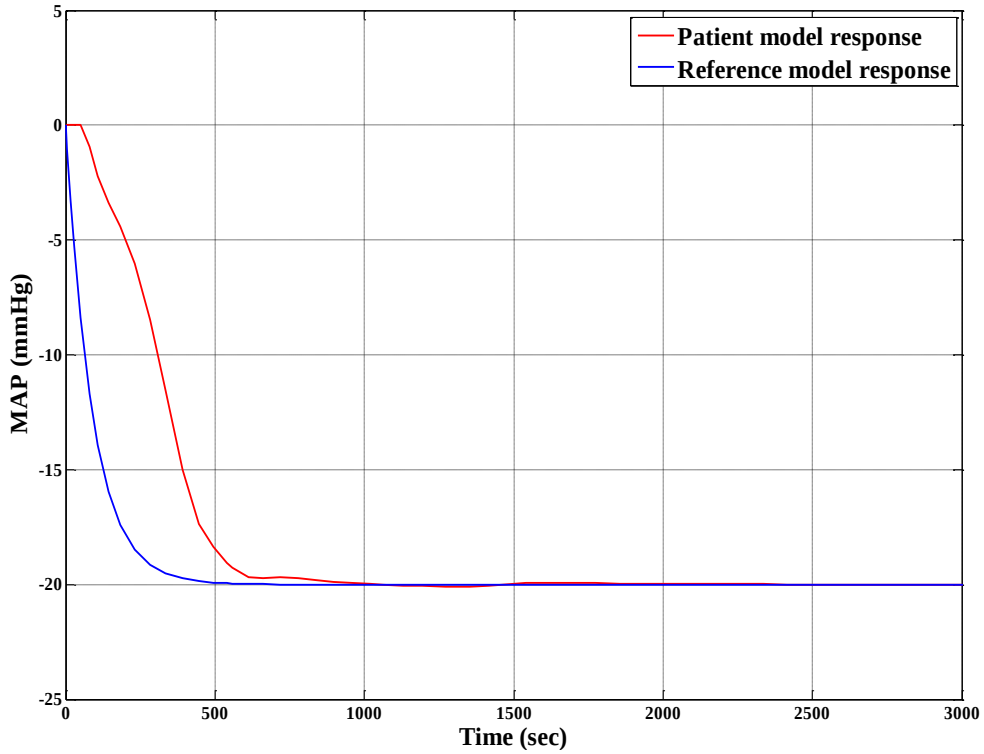



**Figure 5.4: Patient Model and Reference Model Responses without Disturbance, (MAP), $K_{22}$=-15**

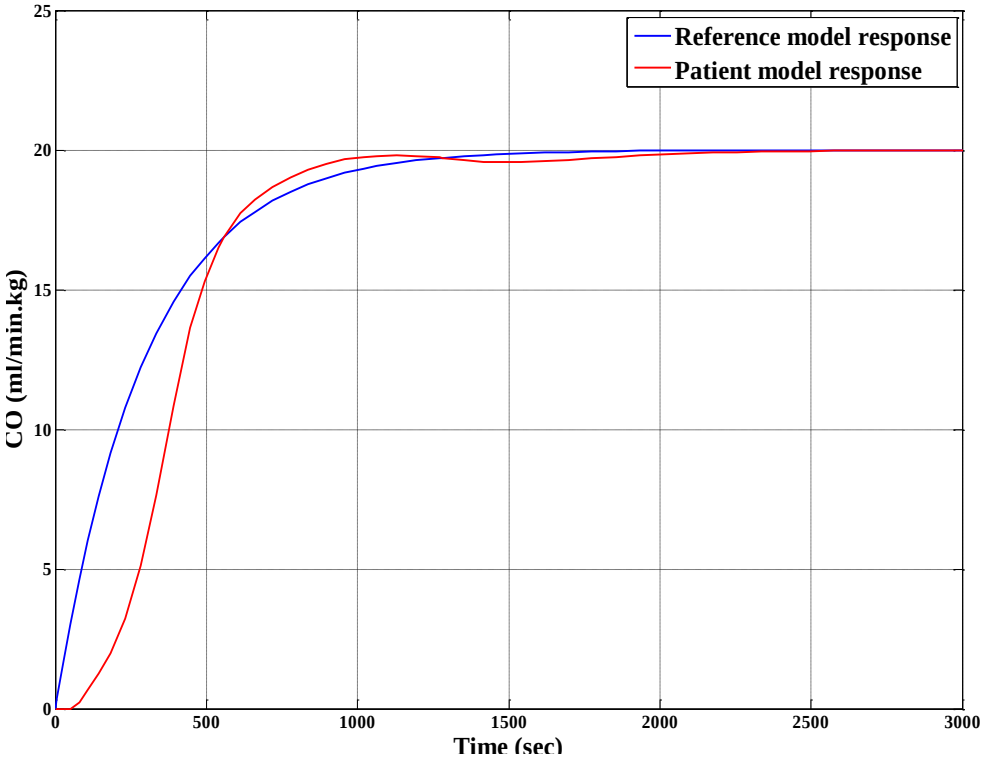



**Figure 5.5: Patient Model and Reference Model Responses without Disturbance, (CO), $K_{22}$=-15.**

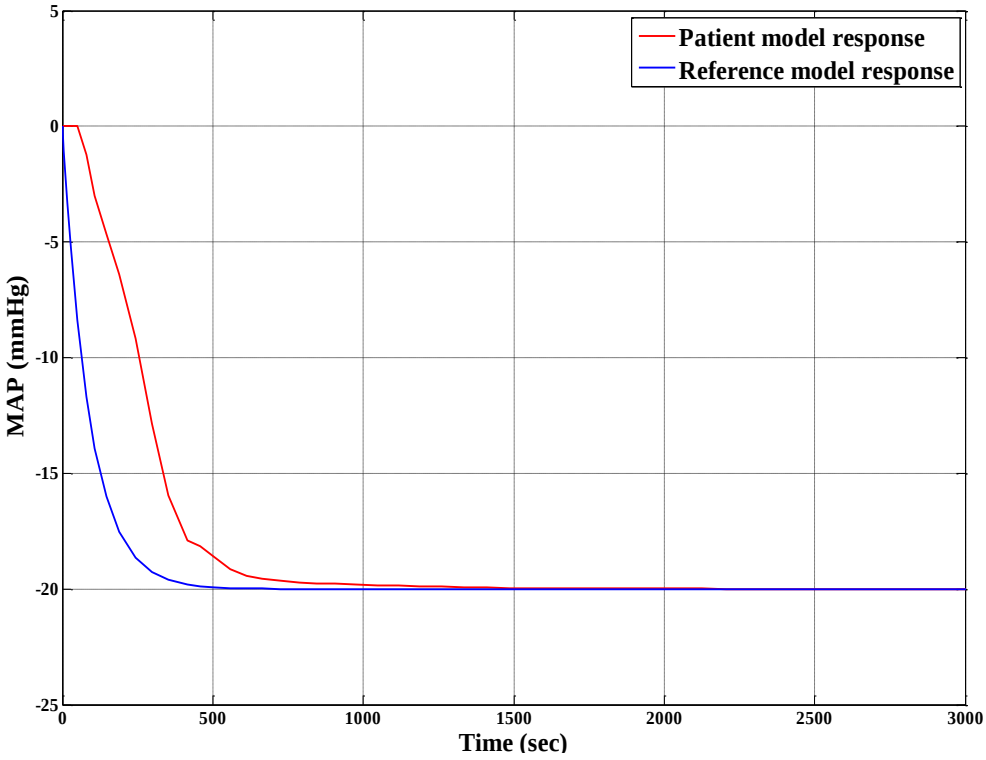



**Figure 5.6: Patient Model and Reference Model Responses without Disturbance, (MAP), $K_{22}$=-20.**

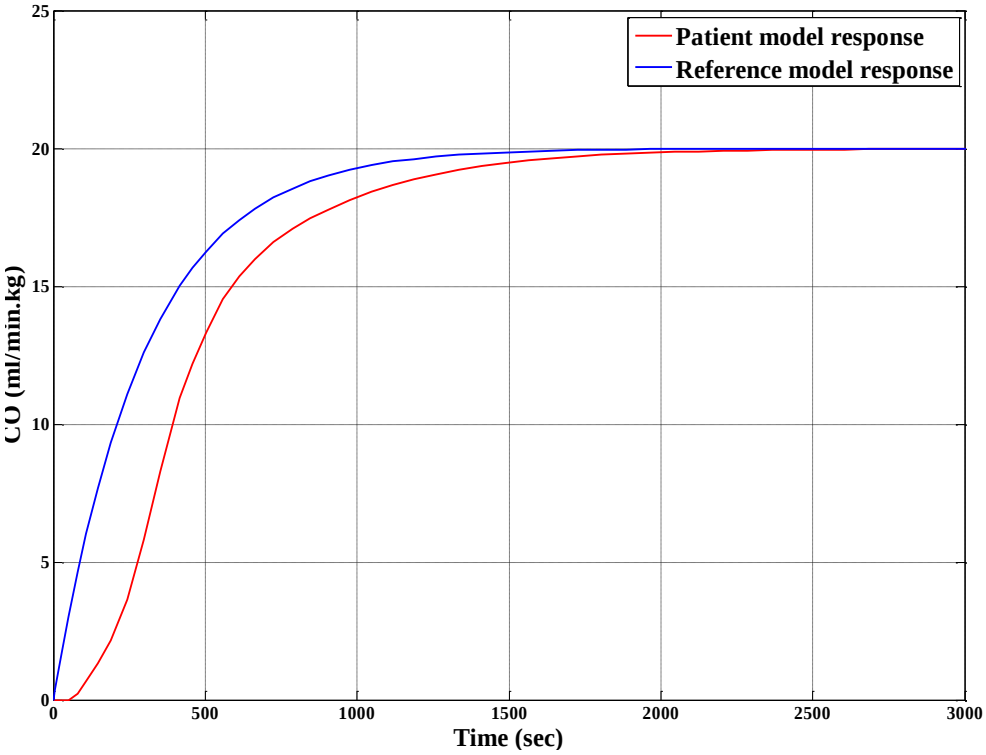



**Figure 5.7: Patient Model and Reference Model Responses without Disturbance, (CO), $K_{22}$=-20.**

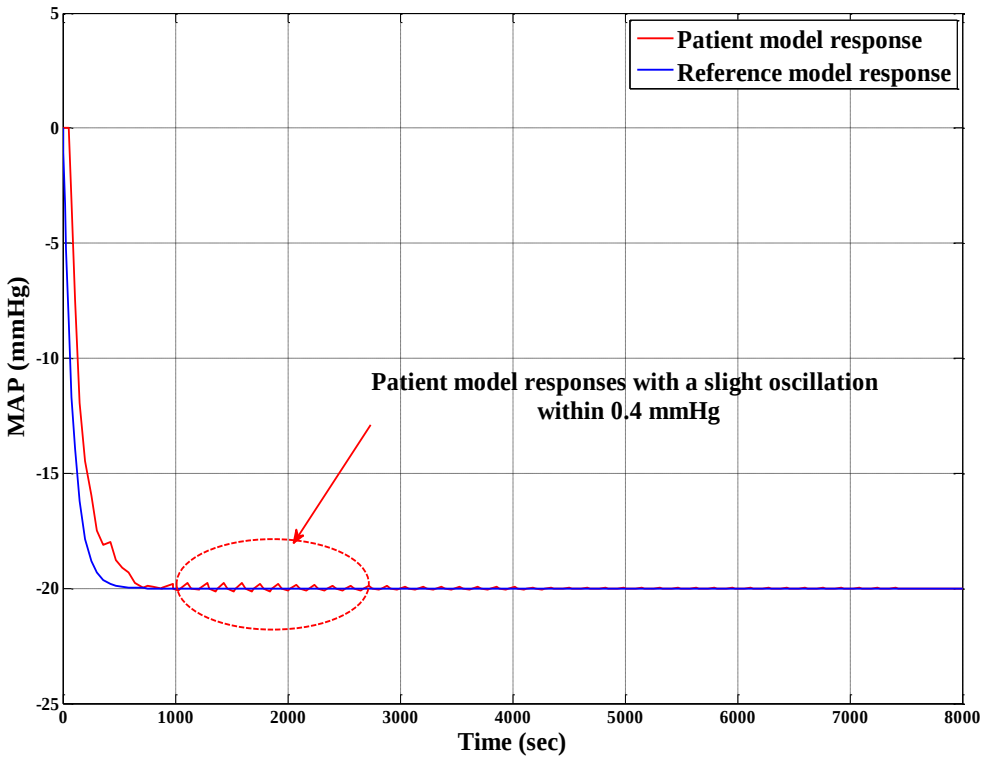



**Figure 5.8: Patient Model and Reference Model Responses without Disturbance, (MAP), $K_{22}$=-50.**

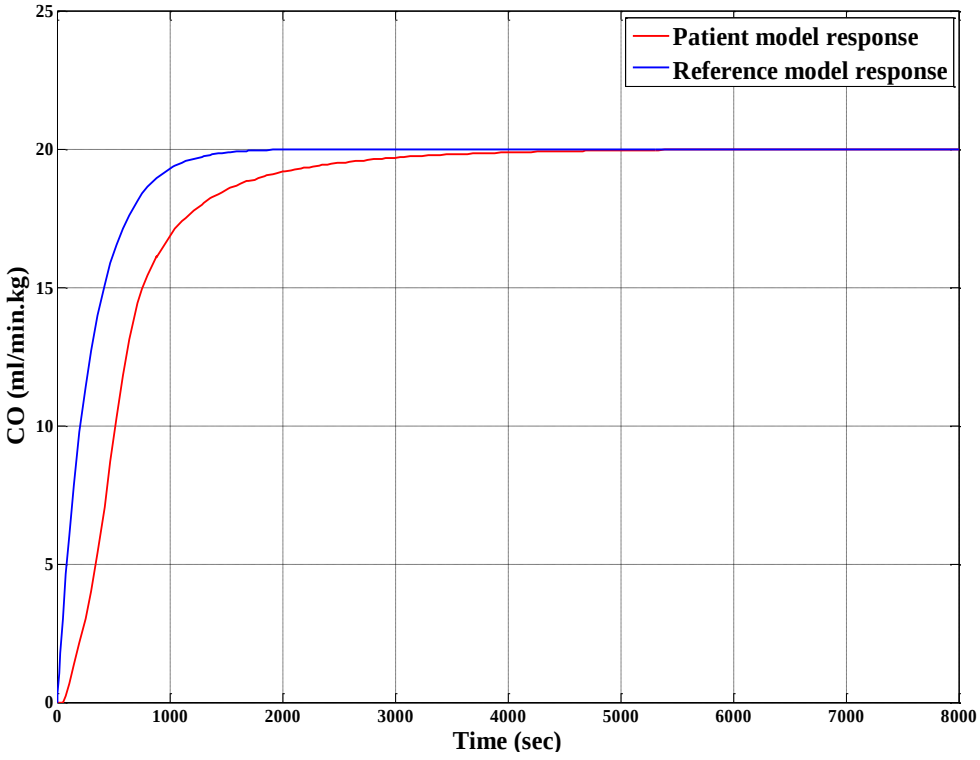



**Figure 5.9: Patient Model and Reference Model Responses without Disturbance, (CO), $K_{22}$=-50.**

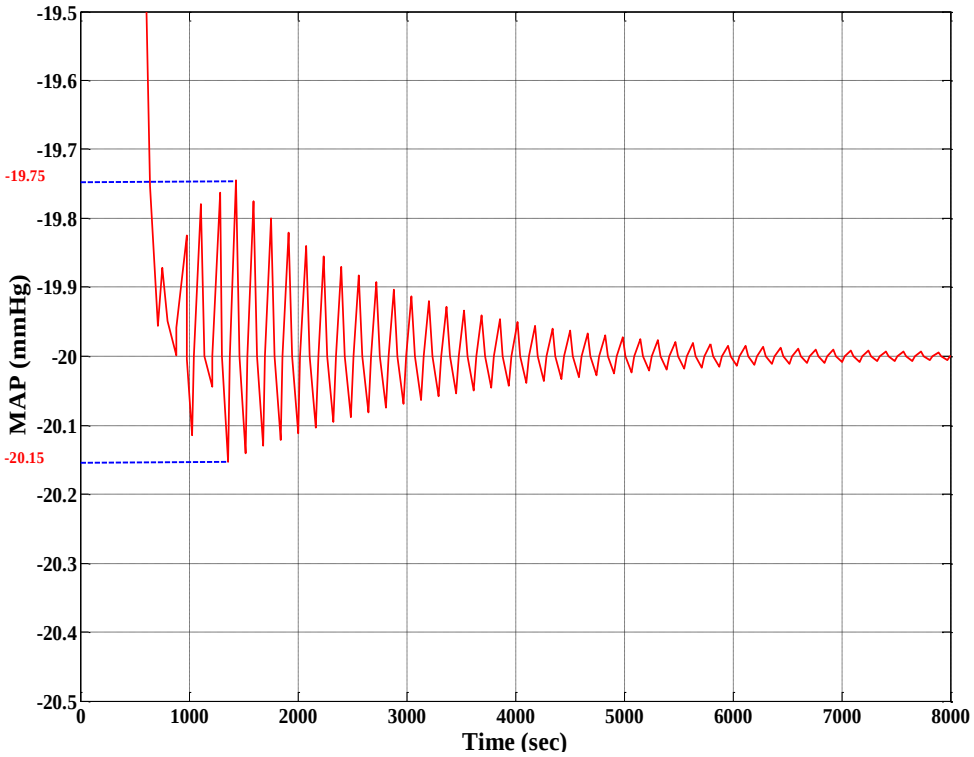



**Figure 5.10: Slight Oscillation of Patient Response Model without Disturbances, (MAP), $K_{22}$=-50.**

The MRAC performance was also investigated when both MAP and CO are subject to the effect of disturbances. We have employed white noise as part of the disturbance model with variance values that D1 and D2 of 0.01, 0.02 and 0.03. The control objective is to maintain MAP and CO at -20 and CO is 20. The results are presented in **Table** 5-5 and depicted in **Figure** 5.11, **Figure** 5.12, **Figure** 5.13 and **Figure** 5.14.These results demonstrate that the controller copes well with disturbances in the hemodynamic responses. The changes in MAP and CO are very small and the infusion rates are well within the safe range.

**Table 5-5: Simulation Results with and without Disturbances, $K_{22}$ Equal -20.**

| *Without Disturbances* | | | | *With Disturbances* | | | | |
|---|---|---|---|---|---|---|---|---|
| **MAP** *"mmHg"* | **CO** *"ml/min.kg"* | **SNP** *"µg/min.kg"* | **DPM** *"µg/min.kg"* | **$D_1$&$D_2$** | **MAP** *"mmHg"* | **CO** *"ml/min.kg"* | **SNP** *"µg/min.kg"* | **DPM** *"µg/min.kg"* |
| - 20 | 20 | 1.176 | 1.176 | 0.001 | - 20.16 | 19.85 | 1.168 | 1.186 |
| | | | | 0.002 | - 20.23 | 19.79 | 1.165 | 1.191 |
| | | | | 0.003 | - 20.28 | 19.75 | 1.162 | 1.194 |

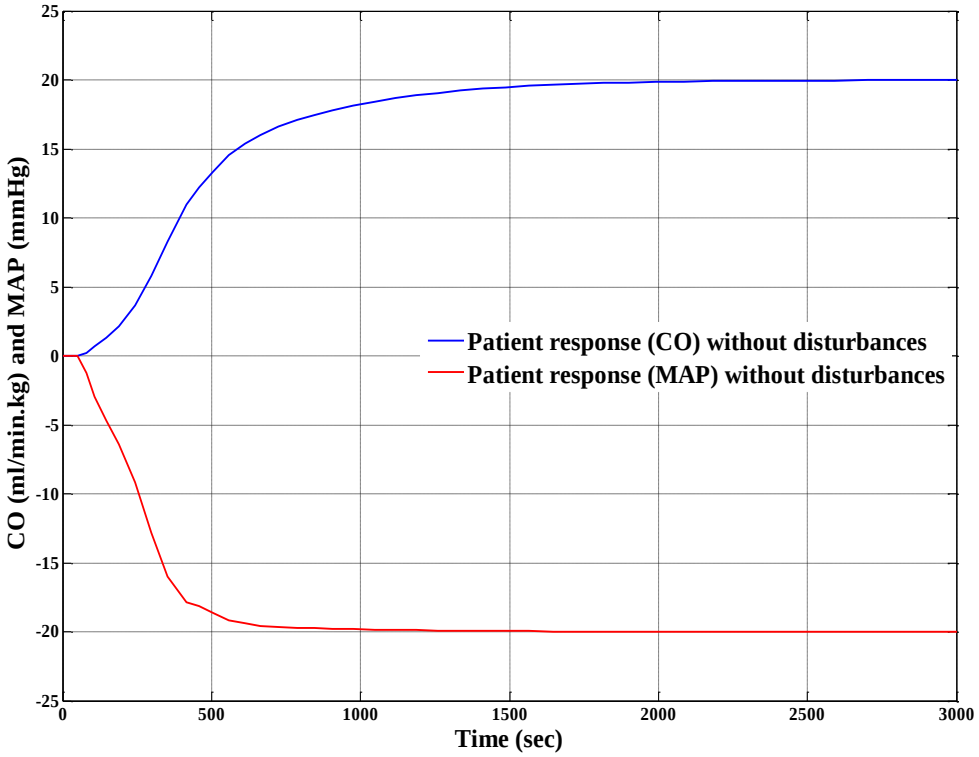



**Figure 5.11: Patient Model Responses without Disturbances, $K_{22}$=-20.**

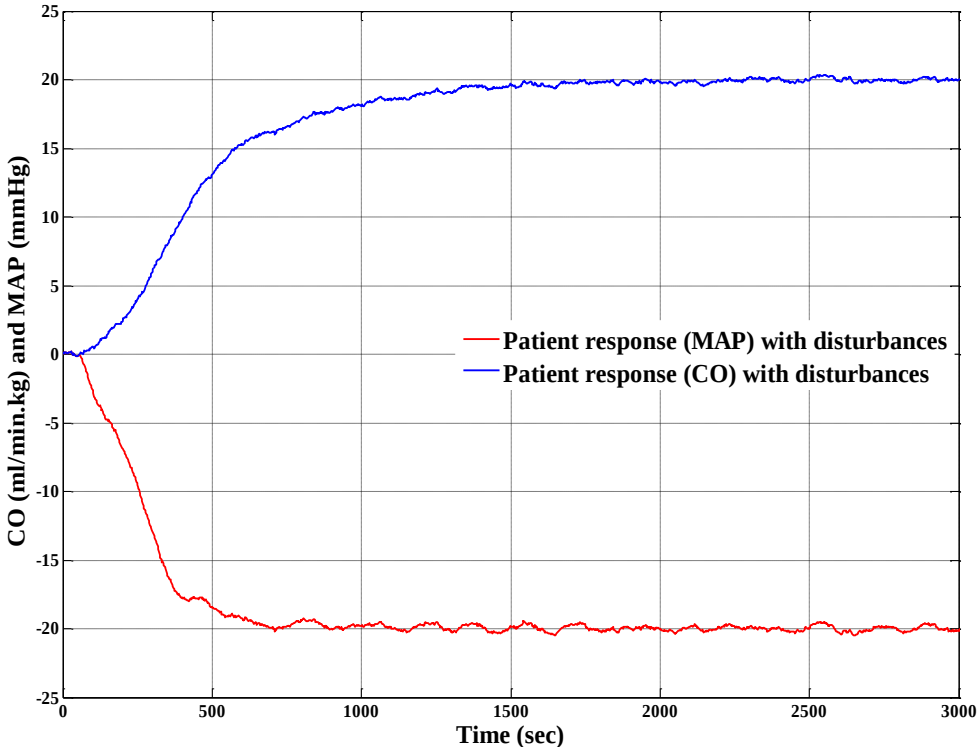



**Figure 5.12: Patient Model Responses with Disturbances 0.01, $K_{22}$=-20.**

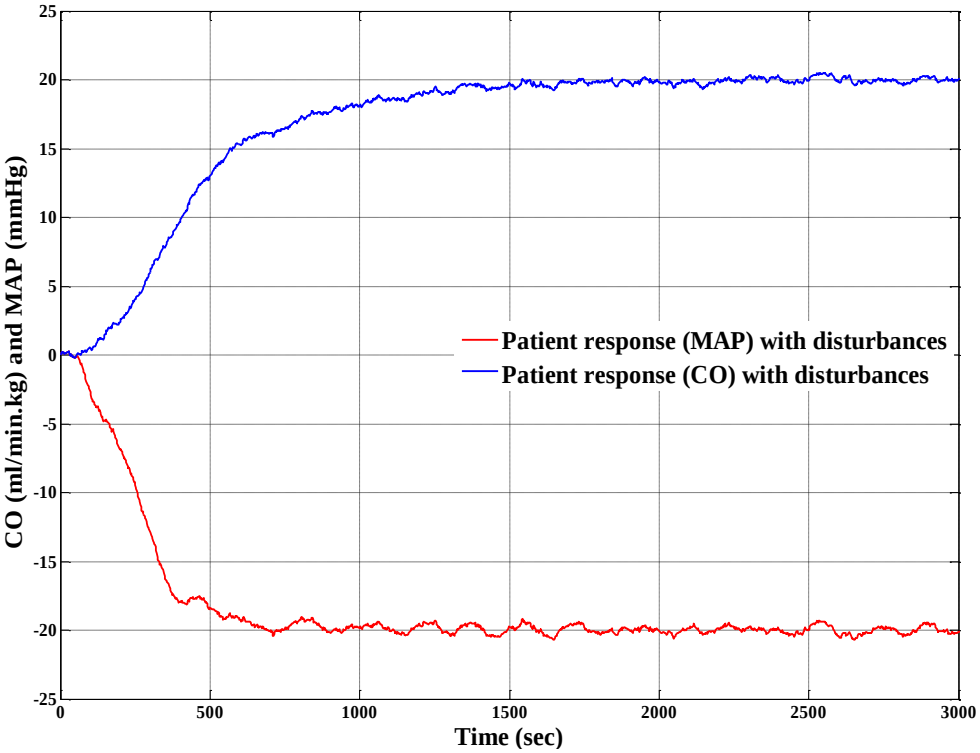



**Figure 5.13: : Patient Model Responses with Disturbances 0.02, $K_{22}$=-20.**

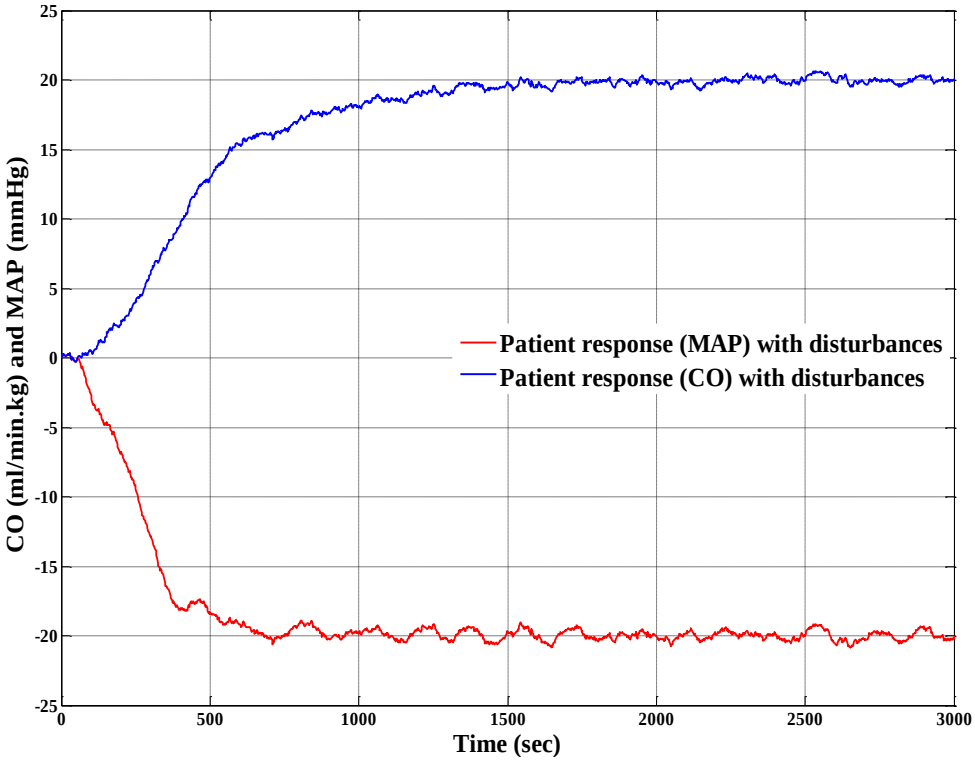



**Figure 5.14: Patient Model Responses with Disturbances 0.03, $K_{22}$=-20.**

## 5.5 Summary

In this chapter we implemented a MIMO control system using two interacting drugs to control both MAP and CO of patients with different sensitivity. A multivariable MRAC algorithm is developed using a two-input, two-output patient model. The control objective is to maintain the hemodynamic variables MAP and CO at the normal values by simultaneously administering two drugs; SNP and DPM. Computer simulations were carried out to investigate the performance of this controller. The results show that the proposed adaptive scheme is robust with respect to disturbances and variations in model parameters.

The proposed scheme was designed and evaluated by simulating variations in patient sensitivity and disturbances in CO and MAP. The

simulation results have confirmed that MRAC is potentially useful for regulating MAP and CO by computing the DPM and SNP infusion rates. The proposed algorithm demonstrated better performance as compared to a non-adaptive PID controller. In these simulation studies the proposed scheme produced better performance compared to reported results, particularly for the updated controller's gain $K_{22}$ (mean arterial pressure gain). This includes shorter settling time and very small or no overshoot when the patient sensitivity $K_{22}$ less than or equal -20.

In **Chapter** 6 we will present an investigation into the design and development of a Neuro-PID control scheme for hemodynamic variables control using two drugs.

# Chapter 6.

## ADAPTIVE MULTI-DRUG NEURO-PID CONTROL SCHEME FOR BLOOD PRESSURE CONTROL

### 6.1 Introduction

The adaptive controller based on the Generalized Fuzzy Neural Network (GFNN) has been applied to control MAP using SNP in 2003 by Er and Gao [111]. In 2006, Kashihara presented the implementation of a multiple adaptive predictive control based on neural networks to maintain the unanticipated responses to drugs of CO and MAP [75]. In 2000 Shu and Pi have used PID controller based on neural network to control time-delay systems, proposed a PID neural network which consists of three layers where the hidden layer's units are proportional, integral and derivative neurons and its weights are adjusted by the back-propagation algorithm [112].

In this chapter we propose a novel Neuro-PID control scheme to regulate MAP and CO using SNP and DPM. The parameters of the PID controller are updated using MATLAB neural network fitting tool (NNFT). The controller parameters are adapted using four inputs and three outputs as patients' sensitivities and controller parameters respectively. The proposed scheme has been implemented, tested and verified to demonstrate its merits and capabilities compared to existing approaches.

## 6.2 Neuro-PID Adaptive Control

Three-term controller, PID has been widely used in the field of process control because of its simplicity and robustness. In conventional PID control, once the well tuned PID gains are obtained, the controller usually exhibits good performance. However, when the dynamic characteristics of the system are time dependent or the operating conditions of the system vary, it is necessary to retune the PID parameters again. This controller has been implemented on patient's model which has been represented in chapter 5 section 5.2 as shown in **Figure** 5.1 to regulate CO and MAP.

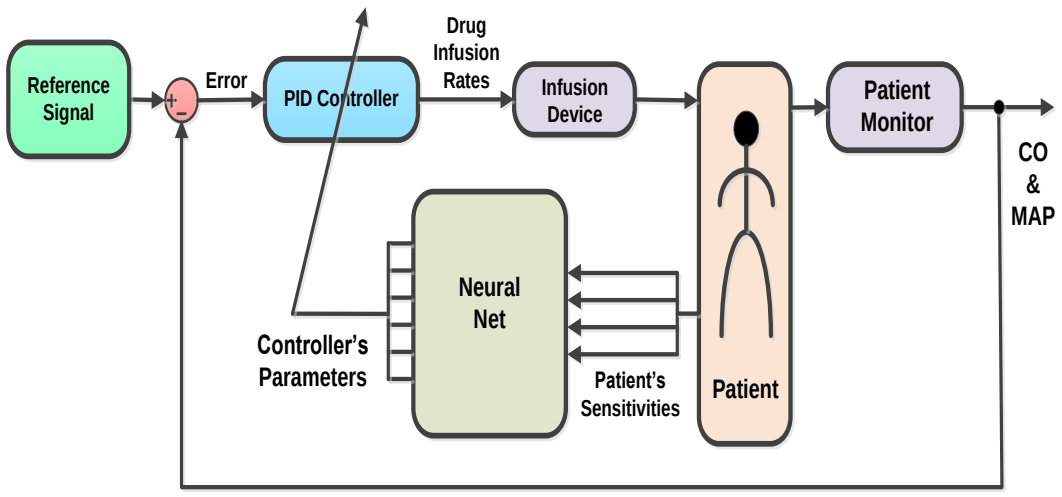



**Figure 6.1: General Form of the Patient's Model with Neural PID Controller.**

The manual tuning of PID controllers is a time-consuming task. To deal with this difficulty, much effort has been invested in developing systematic tuning methods. Many of these methods depend on knowledge of the plant model. Some of these tuning methods are described by Åström et al. in 1995 and 1993 [83, 84]. In this chapter we used Simulink Response to

obtain the optimal initial values of the controller parameters and the neural network is used to tune the PID controller for all types of patient's sensitivities. **Figure** 6.1 above depicts the general form of the system.

Since the patient model has two inputs and two outputs we designed two controllers, the first controller function aims to control the infusion rate of the first drug DPM, and the second controller function is to control the infusion rate of the second drug SNP. The parameters of both controllers are updated by the neural network. **Figure** 6.2 depicts the simulink block diagram of the system. This system has the following:

- One patient model with two inputs and two outputs includes disturbances, the drugs infusion rates represent the inputs and the outputs are the patient's responses to drugs.
- Two PID controllers with three parameters for each one, the first controller is utilized to control the infusion rates of DPM, and the second one is used to control SNP infusion rates.
- The training neural network model. This model has four inputs and six outputs, normalization inputs data model and de-normalisation outputs data model.
- Two set-points, one represents the desired level of CO and the other represents the desired level of MAP.

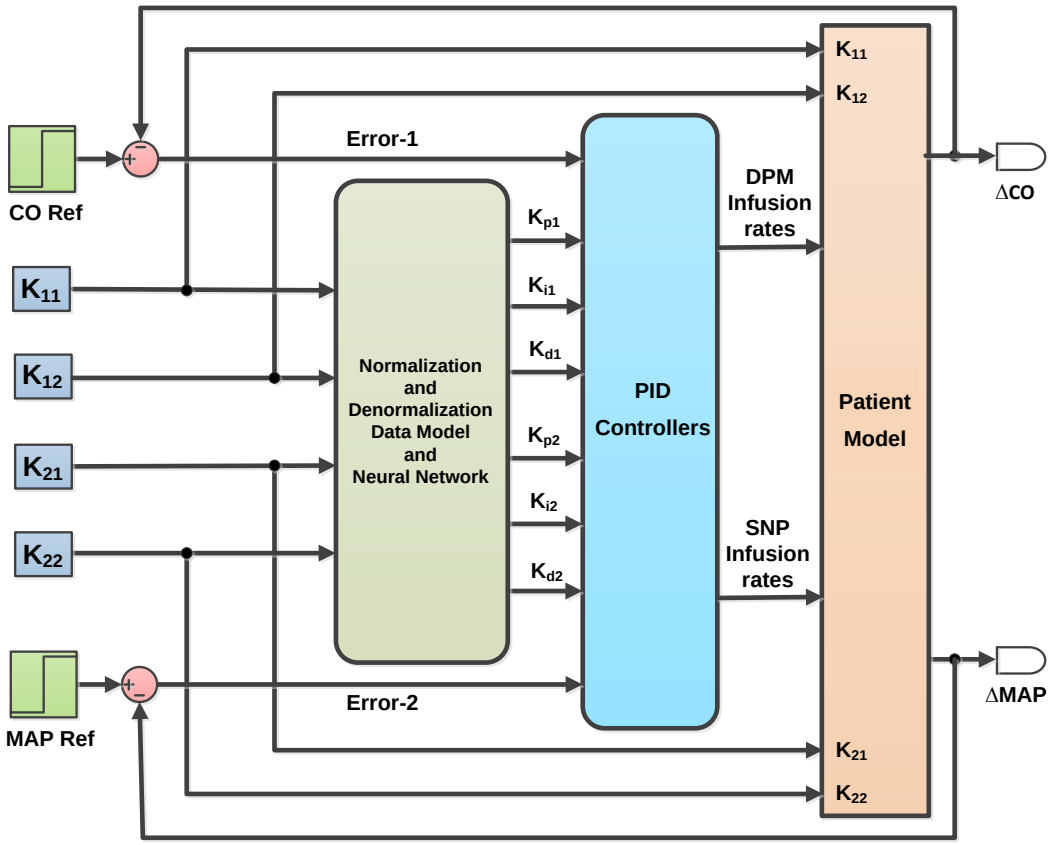



**Figure 6.2: Simulink Block Diagram of the Patient Model with PID Controllers and Neural Networks.**

### 6.2.1 Control Objective

The performance of a Neuro-PID controller is investigated by simulating two hemodynamic variables; MAP and CO. In order to manage the hemodynamic variables, due to the complex, nonlinear behaviour of physiological systems, a good controller is difficult to design. We developed a Neuro-PID controller using NNFT to update the PID controller depending on patients' cases. The data which have been used to train the Neural Network has been obtained from several experiments, to track a reference signal and to optimize the response with uncertainties in the patient's model. The PID controller has been implemented as two SISO controllers with three-

term, proportional, integral and derivative. These terms are represented as controller parameters, $K_p$, $K_i$, and $K_d$. The objectives of the proposed algorithm are:

- Regulate two hemodynamic variables, MAP and CO by the automated infusion rates of inotropic and vasoactive drugs which have been used to decrease MAP and to increase CO, up to desired values.
- Infused suitable amounts of SNP and DPM within in order to achieve the desired level of the hemodynamic variables with settling times and overshoot criteria which has been presented in chapter 4 section 4.3.

With the participation of the neural network, PID controller can simulate online MAP and CO and obtain the optimal infusion rates of the drugs and cover wide range of patient's cases.

### 6.2.2 Control Parameters Optimisation

In this section we employed the Response Optimisation (RO) from Simulink Design Optimisation Technique (SDOT) to obtain the optimal values of PID parameters that $K_p$, $K_i$, and $K_d$.

The simulink block diagram of the system shown in **Figure** 6.3 includes the patient's model, two PID controllers, two step points (CO reference signal. and MAP reference signal), and two signal constraints used to track the reference signals. **Figure** 6.4 depicts the structure of the PID controller.

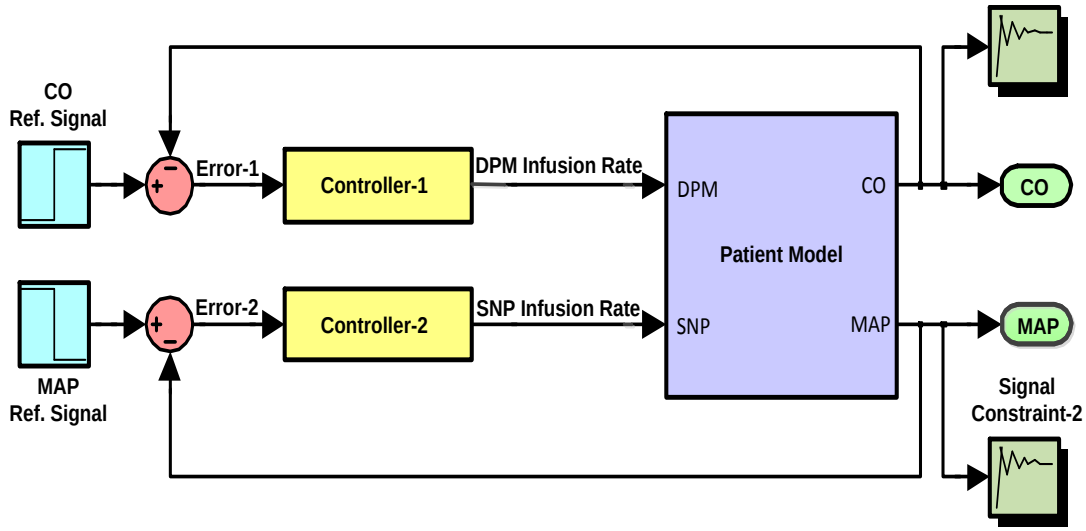



**Figure 6.3: Simulink Block Diagram of the Process of Optimisation.**

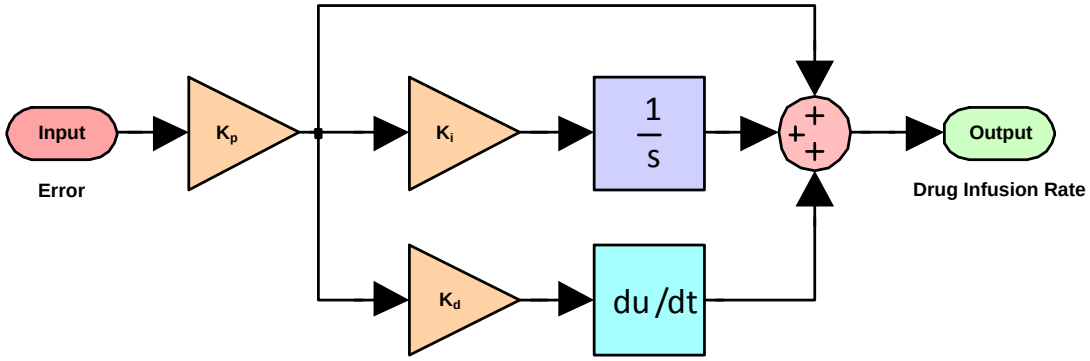



**Figure 6.4: Simulink Block Diagram of PID Controller.**

The optimisation operation shows how to obtain the optimal values of PID parameters to meet the model output reference signal for CO and MAP. The steps of the optimisation's operation are shown in the following Figures and we have considered case number 1 with the values of the patient's sensitivities to drugs as in **Table** 6-2 to show how we obtain the optimal values of the PID parameters. The full system is built by Simulink and optimised as shown in **Figure** 6.5. The PID initial parameters have been chosen as -1 for each parameter and written in an M-file. These values and the optimisation results are presented in **Table** 6-1. **Figure** 6.6 shows the

results of optimisation process for signal constraint of MAP and CO, the constraints which have been used in the simulation are between 478 and 500 seconds for the settling time and 20% from the desired level of CO and MAP for overshoot. **Figure** 6.7 shows the optimal values of the controllers' parameters which have been obtained

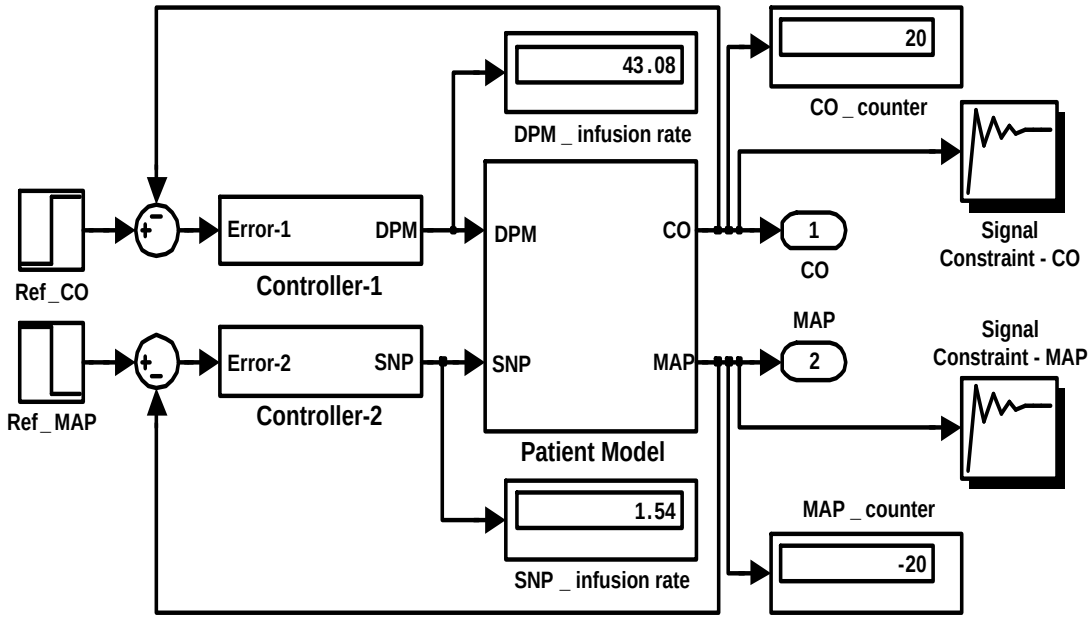



**Figure 6.5: Simulink Block Diagram of the System used for Optimisation with Result of case 1.**

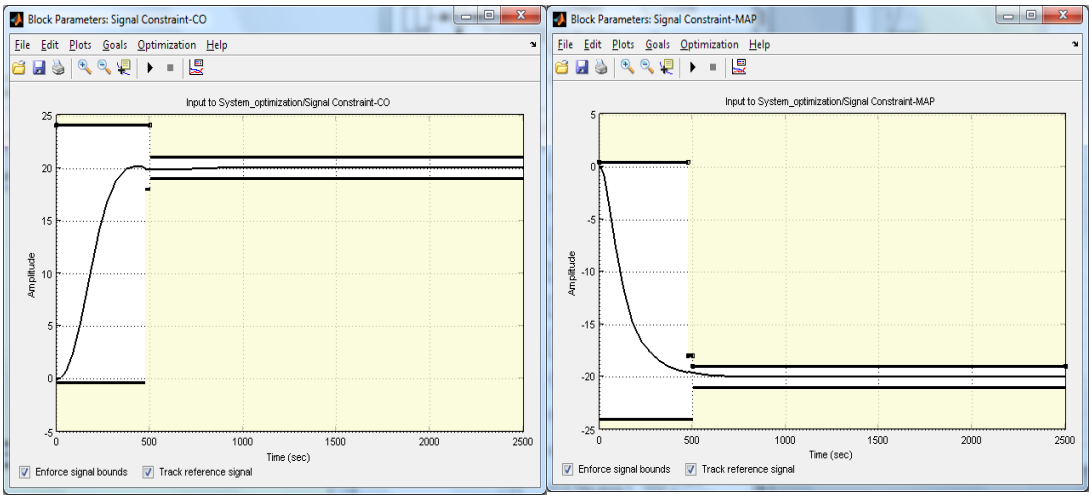



**Figure 6.6: The signal results of optimisation process.**

```
 Iter   S-count      MeshSize          f(x)   Method
Successful termination.
Found a feasible solution within the specified constraint tolerances.

kp1 =

    0.1822


ki1 =

    0.0629


kd1 =

    0.1415


kp2 =

   -0.0098


ki2 =

    0.0540


kd2 =

    1.0049
```

**Figure 6.7: The Output of of Optimisation Results.**

**Table 6-1: The Initial and Optimisation Resultes of the Values of PID Controllers Parameters.**

| Initial Values | | | | | | Optimisation Results | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| $K_{p1}$ | $K_{i1}$ | $K_{d1}$ | $K_{p2}$ | $K_{i2}$ | $K_{d2}$ | $K_{p1}$ | $K_{i1}$ | $K_{d1}$ | $K_{p2}$ | $K_{i2}$ | $K_{d2}$ |
| -1 | -1 | -1 | -1 | -1 | -1 | 0.1822 | 0.0629 | 0.1415 | -0.0098 | 0.054 | 1.0049 |

The optimisation results achieved satisfactory performance and reached the desired level of MAP and CO. MAP decreases by 20 mmHg from the initial value and CO increases by 20 ml/min.kg from the initial value with optimal values of drug infusion rates. The parameters of PID were optimised offline to cover the wide range of patient's sensitivities to drugs using Simulink Response. We have covered 12 patients' cases based on the range values of the patient's model parameters which are given in **Table** 5-1 in chapter 5, section 5.2, and the details of these cases are presented in **Table** 6-2. The optimisation results are presented in **Table** 6-3.

**Table 6-2: The Details of Patient's Cases.**

| Cases | $k_{11}$ | $\tau_{11}$ | $T_{11}$ | $k_{12}$ | $\tau_{12}$ | $T_{12}$ | $k_{21}$ | $\tau_{21}$ | $T_{21}$ | $k_{22}$ | $\tau_{22}$ | $T_{22}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **1** | 1 | 70 | 15 | -15 | 70 | 15 | 0 | 30 | 15 | -13 | 30 | 15 |
| **2** | 2 | 70 | 15 | -7 | 70 | 15 | 1 | 30 | 15 | -13.5 | 30 | 15 |
| **3** | 3 | 70 | 15 | 2 | 70 | 15 | 1.5 | 30 | 15 | -14 | 30 | 15 |
| **4** | 4 | 70 | 15 | 8 | 70 | 15 | 2 | 30 | 15 | -14.5 | 30 | 15 |
| **5** | 5 | 300 | 60 | 12 | 150 | 50 | 3 | 40 | 60 | -15 | 40 | 50 |
| **6** | 6 | 300 | 60 | 12.2 | 150 | 50 | 4 | 40 | 60 | -18 | 40 | 50 |
| **7** | 7 | 300 | 60 | 12.4 | 150 | 50 | 5 | 40 | 60 | -20 | 40 | 50 |
| **8** | 8 | 300 | 60 | 12.6 | 150 | 50 | 5.5 | 40 | 60 | -25 | 40 | 50 |
| **9** | 9 | 600 | 60 | 12.7 | 600 | 60 | 6 | 60 | 60 | -30 | 60 | 60 |
| **10** | 10 | 600 | 60 | 12.8 | 600 | 60 | 7 | 60 | 60 | -38 | 60 | 60 |
| **11** | 11 | 600 | 60 | 12.9 | 600 | 60 | 8 | 60 | 60 | -45 | 60 | 60 |
| **12** | 12 | 600 | 60 | 13 | 600 | 60 | 9 | 60 | 60 | -50 | 60 | 60 |

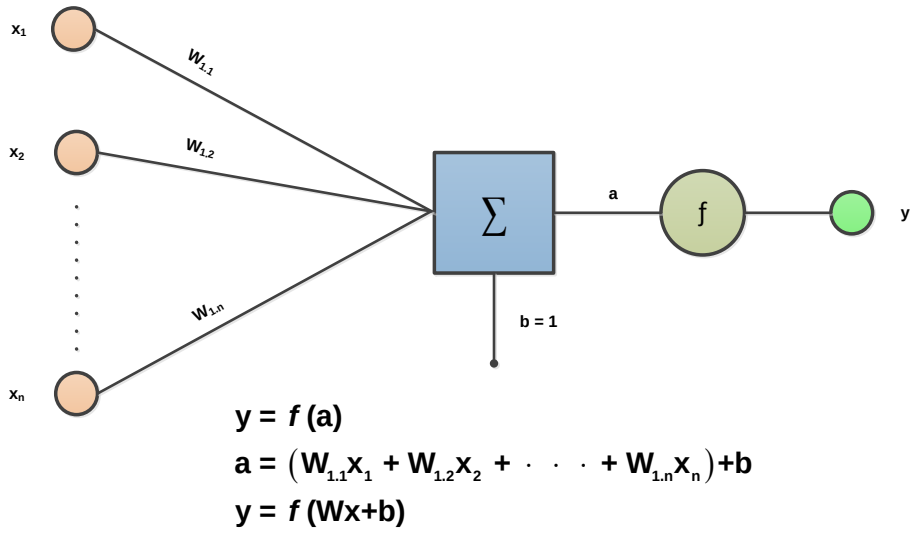
**Table 6-3: The Optimal Values of Controller's Parameters.**

| cases | $k_{p1}$ | $k_{i1}$ | $k_{d1}$ | $k_{p2}$ | $k_{i2}$ | $k_{d2}$ |
|---|---|---|---|---|---|---|
| **1** | 0.1822 | 0.0629 | 0.1415 | - 0.0098 | 0.054 | 1.0049 |
| **2** | 0.2307 | 0.028 | 2.9405 | - 0.0184 | 0.0595 | 0.5866 |
| **3** | 0.0263 | 0.0403 | 0.2952 | - 0.0099 | 0.0734 | 0.7434 |
| **4** | 0.116 | 0.005 | - 1.6066 | - 0.0249 | 0.015 | - 0.2066 |
| **5** | 0.000623 | 0.12 | 0.1598 | - 0.0124 | 0.03 | 0.3292 |
| **6** | 0.004 | 0.025 | - 0.3422 | - 0.03 | 0.016 | 0.2911 |
| **7** | 0.0311 | 0.0037 | 1.6602 | 0.0041 | -0.055 | - 2.4946 |
| **8** | 0.0311 | 0.0048 | 1.6602 | 0.0041 | -0.0495 | 2.4946 |
| **9** | 0.2309 | 0.00102 | 0.6217 | - 0.045 | 0.0046 | 0.8003 |
| **10** | 0.235 | 0.00107 | 0.85 | - 0.045 | 0.0029 | 0.8003 |
| **11** | 0.235 | 0.001225 | 0.85 | - 0.044 | 0.0045 | 3.65 |
| **12** | 0.1999 | 0.0013 | 0.6119 | - 0.0357 | 0.00381 | 0.6908 |

## 6.3 Neural Network Toolbox

The neural network is widely used in fitting functions because of its ability to generalise, respond to unexpected inputs and to learn how to do tasks based on the data given for training. Neural Network Toolbox supports supervised and unsupervised network architectures. In this chapter the supervised networks have been used to retune the controller parameter. There are four types of supervised networks, feedforward, radial basis, dynamic and learning vector quantization.

We have designed and utilised the neural network to make the controller able to work online and cover the wide range of patients. The supervised learning feedforward neural networks have been employed. The components of this neural network are four inputs and six outputs with three layers that input layer with four 4 neurons, hidden layer with twenty 20 neurons and output layer with six 6 neurons. **Figure** 6.8 depicts the general structure of neural network. **Figure** 6.9 displays the structure of three layer feedforward neural network with one hidden layer. The first layer contains three input neurons, second is hidden layer with three neurons, and the third layer contains three output neurons. **Appendix B Figure** 7-1 to **Appendix B Figure** 7-5 shows the neural network model that has been obtained and implemented. The patient's sensitivities to drugs DPM and SNP have been considered as inputs which are represented by $K_{11}$, $K_{12}$, $K_{21}$, and $K_{22}$. The PID parameters $k_p$, $k_i$ and $k_d$, have been considered as outputs to make the PID controller update.




$$y = f(a)$$

$$a = (W_{1.1}x_1 + W_{1.2}x_2 + \cdots + W_{1.n}x_n) + b$$

$$y = f(Wx+b)$$

**Figure 6.8: Block Diagram of General Structure of Neural Network.**

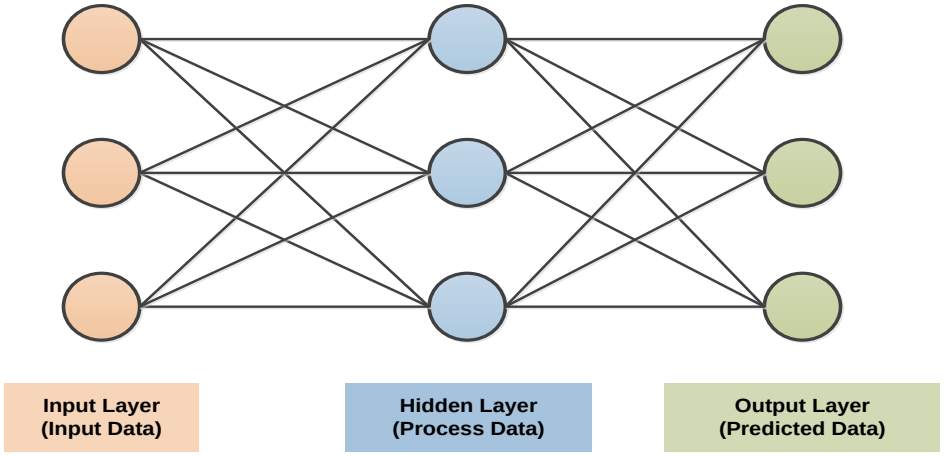



**Figure 6.9: Block Diagram of Structure of Three Layer Feedforward Neural Network.**

### 6.3.1 Procedure of training a neural network

In order to make the PID controller update based on the patient's condition, the neural network has been utilized. In the process of training a neural network, there are six steps to be made:

1. Assemble and Normalize the data
2. Create a Network project
3. Creating a Training Set

4. Create a neural network
5. Train the network
6. Test the network to make sure that it is trained properly

In neural network learning, data with different scales often lead to the instability of neural networks. The data that has been collected has different scales, due to that the data shown in **Table** 6-2 and **Table** 6-3 have been normalised and scaled between 0 and 1 using **Equation** (6.1). The data in **Table** 6-5 and **Table** 6-6 are inputs and outputs of neural network respectively. **Table** 6-4 lists minimum and maximum values of the parameters.

$$X_{i\_new} = \frac{X_i - X_{Min}}{X_{Max} - X_{Min}} \tag{6.1}$$

where,

Xi_new = the data point, normalised between (0-1).

Xi = each data point.

$X_{Min}$ = the minimum among all the data points.

$X_{Max}$ = the maximum among all the data points.

In this part, we have took the data set of patient's cases from the following **Tables** 6-2 and 6-3 to present the process of data normalisation, and the results are shown in **Table** 6-5, **Table** 6-6 and **Table** 6-7. From the data sets presented in **Table** 6-2 and **Table** 6-3 we have identified the Maximum and Minimum values of the patient's sensitivities parameters and

the controller's parameters as shown in **Table** 6-4. The neural network training procedure is presented in appendix A.

**Table 6-4: Maximum and Minimum Values of Inputs and Outputs Parameters.**

| **Patients' sensitivities parameters** | | | |
|---|---|---|---|
| $K_{11\_Max}$ | 12 | $K_{11\_Min}$ | 1 |
| $K_{12\_Max}$ | 13 | $K_{12\_Min}$ | - 15 |
| $K_{21\_Max}$ | 9 | $K_{21\_Min}$ | 0 |
| $K_{22\_Max}$ | - 13 | $K_{22\_Min}$ | - 50 |
| **Controllers' parameters** | | | |
| $K_{p1\_Max}$ | 0.235 | $K_{p1\_Min}$ | 0.000623 |
| $K_{i1\_Max}$ | 0.12 | $K_{i1\_Min}$ | 0.00102 |
| $K_{d1\_Max}$ | 2.9405 | $K_{d1\_Min}$ | - 1.6066 |
| $K_{p2\_Max}$ | 0.0041 | $K_{p2\_Min}$ | - 0.045 |
| $K_{i2\_Max}$ | 0.0734 | $K_{i2\_Min}$ | - 0.055 |
| $K_{d2\_Max}$ | 3.65 | $K_{d2\_Min}$ | - 2.4946 |

**Table 6-5: Data Sets Normalisation Results of Patients' Sensitivities "Inputs".**

| **Cases** | $k_{11\_new}$ | $k_{12\_new}$ | $k_{21\_new}$ | $k_{22\_new}$ |
|---|---|---|---|---|
| **1** | 0 | 0 | 0 | 1 |
| **2** | 0.0909090909090909 | 0.285714285714286 | 0.111111111111111 | 0.986486486486487 |
| **3** | 0.181818181818182 | 0.607142857142857 | 0.166666666666667 | 0.972972972972973 |
| **4** | 0.272727272727273 | 0.821428571428571 | 0.222222222222222 | 0.959459459459459 |
| **5** | 0.363636363636364 | 0.964285714285714 | 0.333333333333333 | 0.945945945945946 |
| **6** | 0.454545454545455 | 0.971428571428571 | 0.444444444444444 | 0.864864864864865 |
| **7** | 0.545454545454545 | 0.978571428571429 | 0.555555555555556 | 0.810810810810811 |
| **8** | 0.636363636363636 | 0.985714285714286 | 0.611111111111111 | 0.675675675675676 |
| **9** | 0.727272727272727 | 0.989285714285714 | 0.666666666666667 | 0.540540540540541 |
| **10** | 0.818181818181818 | 0.992857142857143 | 0.777777777777778 | 0.324324324324324 |
| **11** | 0.909090909090909 | 0.996428571428571 | 0.888888888888889 | 0.135135135135135 |
| **12** | 1 | 1 | 1 | 0 |

**Table 6-6: Data Sets Normalisation Results of 1st Controller's Parameters "Outputs".**

| Cases | $k_{p1\_new}$ | $k_{i1\_new}$ | $k_{d1\_new}$ |
|---|---|---|---|
| **1** | 0.774721922372929 | 0.52008740964868 | 0.384442831694926 |
| **2** | 0.98165348989022 | 0.226760800134476 | 1 |
| **3** | 0.109554265136938 | 0.330139519246932 | 0.418244595456445 |
| **4** | 0.492270999287473 | 0.0334510001680955 | 0 |
| **5** | 0 | 1 | 0.388467374810319 |
| **6** | 0.0144084103815647 | 0.201546478399731 | 0.278067339623056 |
| **7** | 0.130034090375762 | 0.0225247940830392 | 0.718435926194717 |
| **8** | 0.130034090375762 | 0.0317700453857791 | 0.718435926194717 |
| **9** | 0.982506815941837 | 0 | 0.490048602405929 |
| **10** | 1 | 0.000420238695579088 | 0.540256427173363 |
| **11** | 1 | 0.00172297865187426 | 0.540256427173363 |
| **12** | 0.850241277941095 | 0.0023533366952429 | 0.4878933825955 |

**Table 6-7: Data Sets Normalisation Results of 2nd Controller's Parameters "Outputs".**

| Cases | $K_{p2\_new}$ | $K_{i2\_new}$ | $K_{d2\_new}$ |
|---|---|---|---|
| **1** | 0.716904276985743 | 0.848909657320872 | 0.569524460501904 |
| **2** | 0.541751527494908 | 0.891744548286604 | 0.501448426260456 |
| **3** | 0.714867617107943 | 1 | 0.526966767568271 |
| **4** | 0.409368635437882 | 0.545171339563863 | 0.372359470103831 |
| **5** | 0.663951120162933 | 0.661993769470405 | 0.459557985873775 |
| **6** | 0.305498981670061 | 0.552959501557632 | 0.453357419522833 |
| **7** | 1 | 0 | 0 |
| **8** | 1 | 0.0428348909657321 | 0 |
| **9** | 0 | 0.46417445482866 | 0.536226930963773 |
| **10** | 0 | 0.450934579439252 | 0.536226930963773 |
| **11** | 0.0203665987780041 | 0.463395638629283 | 1 |
| **12** | 0.189409368635438 | 0.458021806853583 | 0.518406405624451 |

## 6.4 Experimental Results

Matlab Simulink has been used to simulate the patients' model presented in **Figure** 6.2 and the PID controllers' parameters named $k_{p1}$, $k_{i1}$, $k_{d1}$, $k_{p2}$, $k_{i2}$ and $k_{d2}$ have been tuned using neural networks. **Table** 5-1 in chapter 5 presents the ranges of values of the patient's sensitivity. The patient's sensitivity to drug varies from patient to patient. Due to this, the drug infusion controller should be designed to work well in a real-time environment for a wide range of patients. In the simulation, the automatic multiple drug delivery system simulates MAP and CO using DPM and SNP with different sensitivity. The PID controller based on neural network has been implemented to control the infusion rate of the drugs. The controller has been adapted using the neural network with patients' sensitivities as inputs and controllers' parameters as the outputs to make the controller suitable for a wide range of patients. The system has been tested using different patient's sensitivity, and the parameters' values of the patient's model have included different types of patient's sensitivities to drugs. The patients' sensitivities to DPM have been represented by $K_{11}$ and $K_{12}$. $K_{21}$ and $K_{22}$ have represented the patients' sensitivities to SNP.

Data in **Table** 6-3 represent the optimal values of the PID controllers' parameters which have been obtained by the implementation of SDOT. These results have been relied upon to employ the neural network to control the multi-drug infusion control system and cover the wide range of patients with and without disturbances. From these results we observe that the

proposed algorithm is able to control simultaneously MAP and CO using two drugs. The results demonstrate the controller is able to cover the wide range of patients.

**Table 6-8: Patient Response to DPM and SNP without the Impact of Disturbances.**

| Cases | Patients' sensitivities | | | | DPM *"µg/min.kg"* | SNP *"µg/min.kg"* | CO *"ml/min.kg"* | MAP *"mmHg"* |
|---|---|---|---|---|---|---|---|---|
| | $K_{11}$ | $K_{12}$ | $K_{21}$ | $K_{22}$ | | | | |
| **1** | 1 | -15 | 0 | -13 | 43.08 | 1.54 | 20 | -20 |
| **2** | 2 | -7 | 1 | -13.5 | 20.50 | 3.00 | 20 | -20 |
| **3** | 3 | 2 | 1.5 | -14 | 5.33 | 2.00 | 20 | -20 |
| **4** | 4 | 8 | 2 | -14.5 | 1.76 | 1.62 | 20 | -20 |
| **5** | 5 | 12 | 3 | -15 | 0.54 | 1.44 | 20 | -20 |
| **6** | 6 | 12.2 | 4 | -18 | 0.74 | 1.28 | 20 | -20 |
| **7** | 7 | 12.4 | 5 | -20 | 0.75 | 1.19 | 20 | -20 |
| **8** | 8 | 12.6 | 5.5 | -25 | 0.92 | 1.00 | 20 | -20 |
| **9** | 9 | 12.7 | 6 | -30 | 1.00 | 0.87 | 20 | -20 |
| **10** | 10 | 12.8 | 7 | -38 | 1.07 | 0.72 | 20 | -20 |
| **11** | 11 | 12.9 | 8 | -45 | 1.07 | 0.64 | 20 | -20 |
| **12** | 12 | 13 | 9 | -50 | 1.03 | 0.59 | 20 | -20 |

**Table 6-9: Patient Response to DPM and SNP with the Impact of Disturbances, $D_1$ and $D_2$ = 0.05.**

| Cases | Patients' sensitivities | | | | DPM *"µg/min.kg"* | SNP *"µg/min.kg"* | CO *"ml/min.kg"* | MAP *"mmHg"* |
|---|---|---|---|---|---|---|---|---|
| | $K_{11}$ | $K_{12}$ | $K_{21}$ | $K_{22}$ | | | | |
| **1** | 1 | -15 | 0 | -13 | 43.07 | 1.54 | 19.96 | -20.05 |
| **2** | 2 | -7 | 1 | -13.5 | 20.51 | 3.00 | 19.95 | -20.06 |
| **3** | 3 | 2 | 1.5 | -14 | 5.33 | 2.00 | 19.94 | -20.05 |
| **4** | 4 | 8 | 2 | -14.5 | 1.76 | 1.62 | 19.94 | -20.07 |
| **5** | 5 | 12 | 3 | -15 | 0.54 | 1.44 | 19.95 | -20.05 |
| **6** | 6 | 12.2 | 4 | -18 | 0.74 | 1.27 | 19.94 | -20.03 |
| **7** | 7 | 12.4 | 5 | -20 | 0.75 | 1.19 | 19.94 | -20.05 |
| **8** | 8 | 12.6 | 5.5 | -25 | 0.92 | 1.00 | 19.94 | -20.05 |
| **9** | 9 | 12.7 | 6 | -30 | 1.01 | 0.87 | 19.95 | -19.95 |
| **10** | 10 | 12.8 | 7 | -38 | 1.09 | 0.73 | 19.95 | -19.94 |
| **11** | 11 | 12.9 | 8 | -45 | 1.09 | 0.64 | 19.95 | -19.94 |
| **12** | 12 | 13 | 9 | -50 | 1.04 | 0.59 | 19.95 | -19.92 |

From these results we have selected some cases from **Table** 6-8 and **Table** 6-9 above. These cases are 1, 6, and 12 to show the patients' responses to drug with and without disturbances. The results of simulation demonstrate that the PID controller based on neural network is able to cover different types of patients in real-time with acceptable results.

**Table 6-10: Performances of Neuro-PID Adaptive Control for MAP and CO Regulation.**

| Cases | Settling Time | | Overshoot | |
|---|---|---|---|---|
| | MAP (mmHg) | CO (ml/min.kg) | MAP (mmHg) | CO (ml/min.kg) |
| **1** | 475 | 378 | zero | 0.31 |
| **2** | 416 | 427 | zero | zero |
| **3** | 559 | 810 | zero | zero |
| **4** | 819 | 643 | zero | Zero |
| **5** | 597 | 1183 | zero | zero |
| **6** | 541 | 1514 | zero | zero |
| **7** | 856 | 663 | 1.15 | 0.08 |
| **8** | 801 | 650 | 1.61 | 0.18 |
| **9** | 450 | 588 | 0.38 | 0.04 |
| **10** | 1103 | 649 | zero | zero |
| **11** | 1003 | 486 | 1.21 | 0.01 |
| **12** | 661 | 553 | 0.51 | 0.07 |

**Figure** 6.10, **Figure** 6.11 and **Figure** 6.12, show the simulation results of the patient responses to drug infusion rates. They also, illustrate the response of the patient to DPM and SNP when increase CO of 20 ml/min.kg and decrease MAP of 20 mmHg from the initial values. The results in **Table** 6-10 clearly demonstrate the controller performance is better with less settling time and overshoot compared to the performance of the non-adaptive PID controller in chapter four and with the performance of MRAC in chapter five. In addition this algorithm is able to simulate online MAP and CO by obtaining the optimal infusion rates of the drugs and cover a wide range of patients' cases.

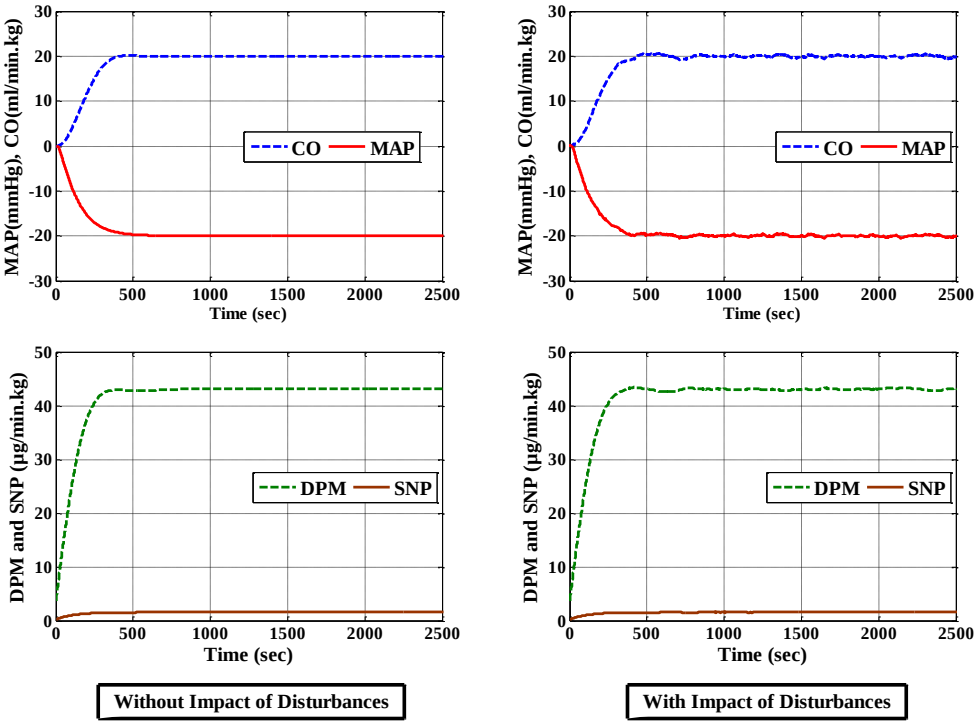



**Figure 6.10: CASE (1) Patient Response (CO and MAP) to drugs (DPM and SNP) with and without the Impact of Disturbances.**

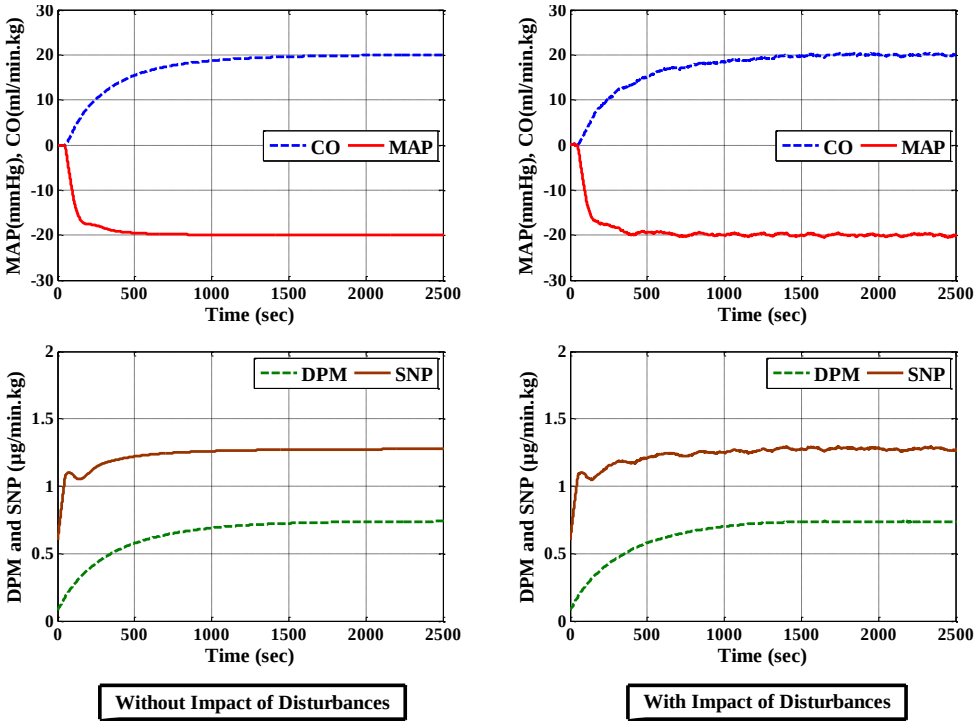



**Figure 6.11: CASE (6) Patient Response (CO and MAP) to drugs (DPM and SNP) with and without the Impact of Disturbances.**

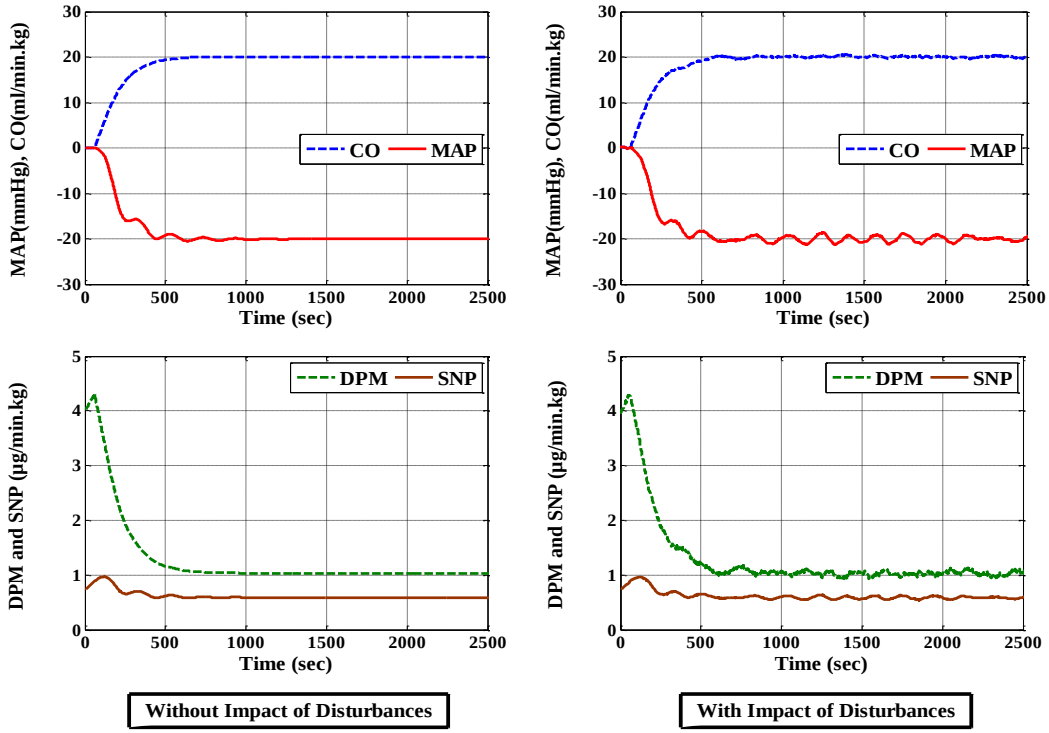



**Figure 6.12: CASE (12) Patient Response (CO and MAP) to drugs (DPM and SNP) with and without the Impact of Disturbances.**

## 6.5 Summary

Control of physiological states such as mean arterial pressure (MAP) has been successfully achieved using single drug by different control algorithms. Multi-drug delivery demonstrates a significantly challenging task as compared to control with a single-drug. Also the patient's sensitivity to the drug varies from patient to patient. Therefore, the implementation of adaptive controller is very essential to improving dealing with the variety of patient physiological responses. This chapter presents the design and implementation of a PID based on neural network. The function of this scheme is to update the PID controller to regulate MAP and CO of the different patients by administering vasoactive and inotropic drugs SNP and

DPM respectively. The parameters of the PID controller were optimised offline using Simulink Response Tool.

This chapter has presented an adaptive multi-drug Neuro-PID control scheme for blood pressure control. The proposed scheme was designed and evaluated in simulation study to maintain the nonlinear responses of CO and MAP using two drugs, namely DPM and SNP for the patients of various sensitivities. The simulation results have confirmed that the PID based on neural network is potentially useful for regulating the MAP and CO. The proposed approach offers much better performance compared to existing approaches to cover a wide range of patients.

# Chapter 7.

## CONCLUSIONS AND FUTURE WORK

### 7.1 Conclusion

The main focus of this thesis was divided in two parts; the first part was to compare the performance of two control strategies which have been considered to achieve the optimal infusion rate of a single drug SNP in order to regulate MAP. The PID and IMC controllers have been implemented to control blood pressure using three types of patient's sensitivities to SNP. The GAs optimization methods have been implemented to find the optimal values of controllers' parameters. The simulation results have demonstrated the PID controller achieved much smaller settling times than the IMC which has been demonstrated in [47, 49]. The sensitive patient response has a little overshoot but this is much less than the performance criteria set in [42].

In the second part of the research work an adaptive multi-drug control scheme was developed and implemented to regulate the patients' MAP and CO by infusing the optimal infusion rates of two drugs SNP and DPM. The MRAC was designed and evaluated by simulating variations in patient sensitivity to drugs and with disturbances in MAP and CO. The simulation results have confirmed MRAC is potentially useful for regulating MAP and CO by computing the DPM and SNP infusion rates. The proposed algorithm demonstrated better performance compared to the non-adaptive PID

controller. In the simulation studies, the proposed scheme produced better performance compared to existing researchers' results, particularly for the updated controller's gain. This includes shorter settling time and very small or no overshoot when the patient sensitivity $K_{22}$ is less than or equal $-20$.

In chapter six an adaptive multi-drug Neuro-PID control scheme for blood pressure control was developed and implemented. The proposed scheme was designed to overcome the problem of having a linear patient model which does reflect the range of dynamics of patients in real-life. The main benefit of the Neuro-PID is its ability to capture the nonlinear responses of MAP and CO to the drugs, DPM and SNP and cope with various patients sensitivities. The simulation results have confirmed that PID controller based on neural network has a good performance and can cope with a wide range of patient.

## 7.2 Limitations of Study

This study focused on the control of mean arterial pressure and cardiac output. Other hemodynamic variables could be incorporated in the control system.

In this study the patient's model that was used was a SISO and MIMO input-output transfer function with time delays. This model does not entirely capture the real-life patient reactions to drugs. In view of this, the neural network system in chapter 6 was developed to capture the variations

## 7.3 Future Work

The simulation results in this thesis have achieved the main objectives, and the algorithms have provided good performance. However, future work may include the following:

- The logical step is to apply and test the SISO and MIMO control systems presented in chapters 4 and 6 in clinical trials using animals.

- Implement interactive MIMO control instead of using two SISO control loops.

- Extend the patients' model to manage more primary physiological parameters of the hemodynamic variables for instance mean pulmonary arterial pressure (MPAP) as the output with more intravenous infusion drug such as phenylephrine (PNP) as input.

- In this research a first order patient's model with time delays was used in the simulations. A better model is obtained by getting real data from patients and using a neural network to obtain a nonlinear model which would describe better the patients' response to various drugs.

# APPENDIXES

## APPENDIX A: NEURAL NETWORK TRAINING PROCEDURE

**Step 1:** The neural network fitting tool with a two-layer feed-forward network, sigmoid hidden neurons and output neurons. The input is a data set of patent's sensitivities to drugs and output is a data set of controller's parameters, as shown in **Appendix A Figure** 7-1.

**Step 2:** Select data of the input and output and inserted as matrix, the inputs data as IN and the outputs data as OUT. **Appendix A Figure** 7-2 illustrates this step.

**Step 3:** Select the percentages for validation and testing data, the rest of percentages will be for training as shown in **Appendix A Figure** 7-3.

**Step 4:** Network size, selecting the numbers of hidden neurons, these numbers have been selected as 20 hidden layers, **Appendix A Figure** 7-4 shows that.

**Step 5:** Train network, the network start training to fit the inputs and outputs, and training progress which present the training results as shown in **Appendix A Figure** 7-5.

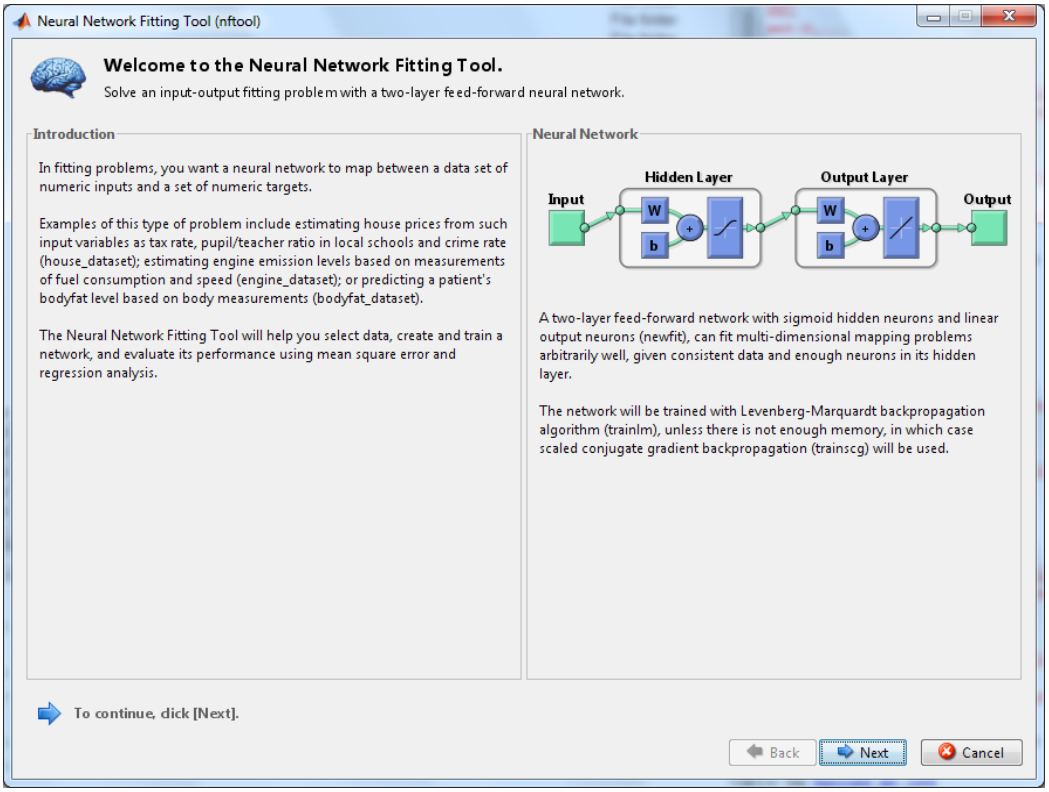
**Step 6:** Present training result by plot and present the best validation performance result as shown in **Appendix A Figure** 7-6.

**Step 7:** Present training result by plot training state as **in Appendix A Figure** 7-7.

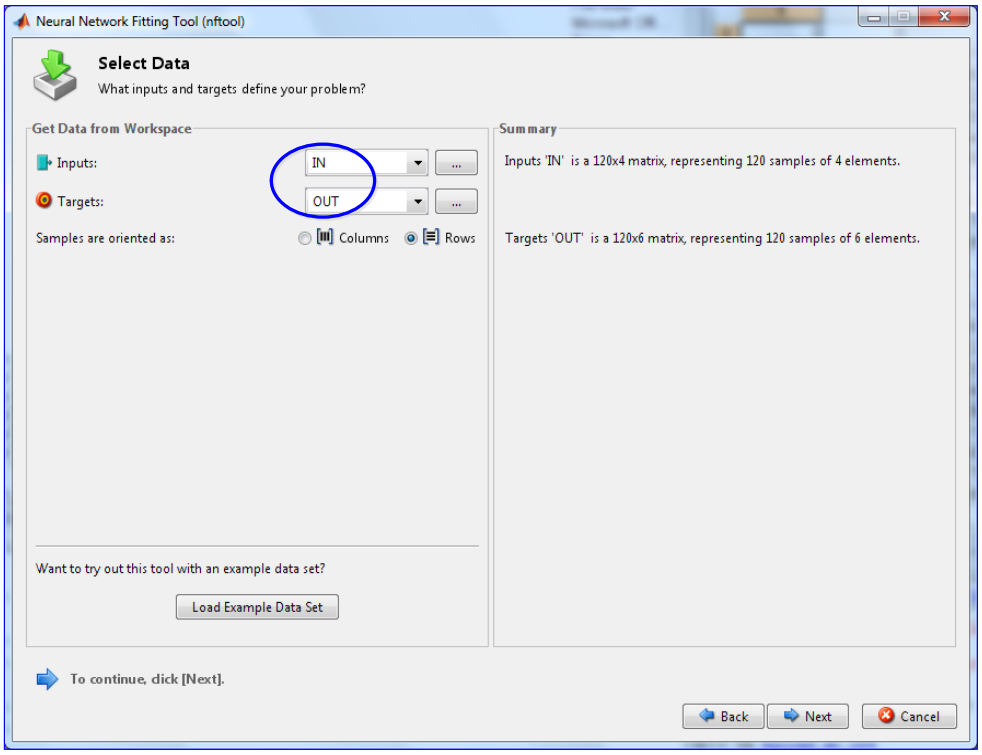
**Step 8:** Present training result by plot of training, validation and test results, the regression (R) values have reach the optimal value as shown in **Appendix A Figure** 7-8.

**Step 9:** Present training result by plot of regression, the result of this step has reach the optimal value of regression, as shown in **Appendix A Figure** 7-9.

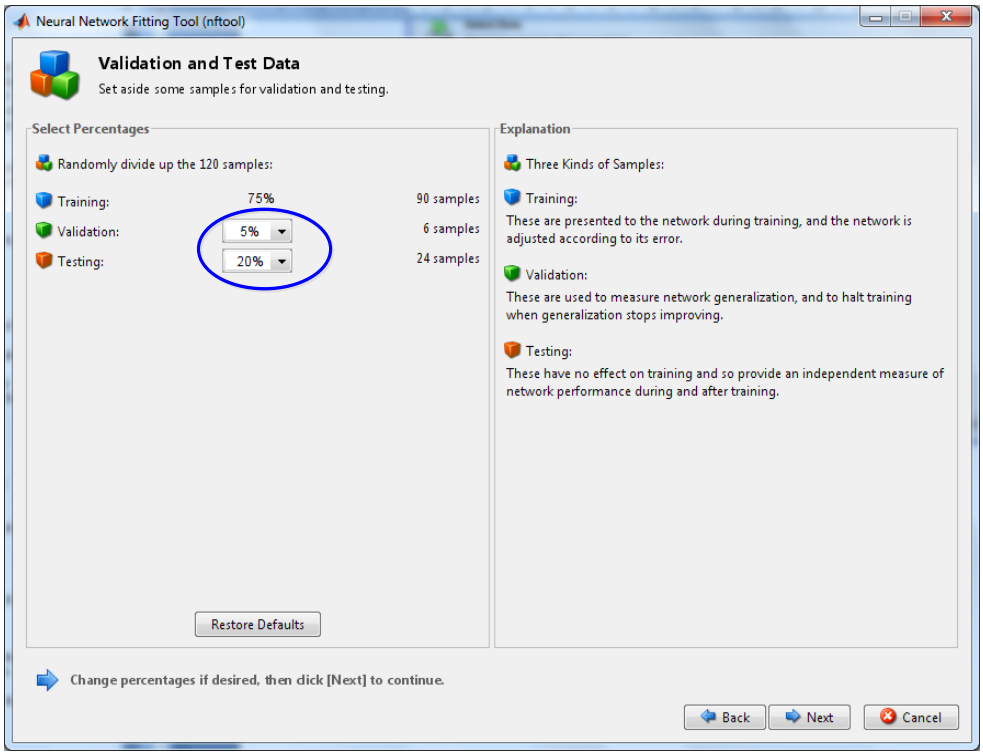
**Step 10:** Save network training results as simulink file, the neural network simulink model has shown in **Appendix A Figure** 7-10 and employed in the system.



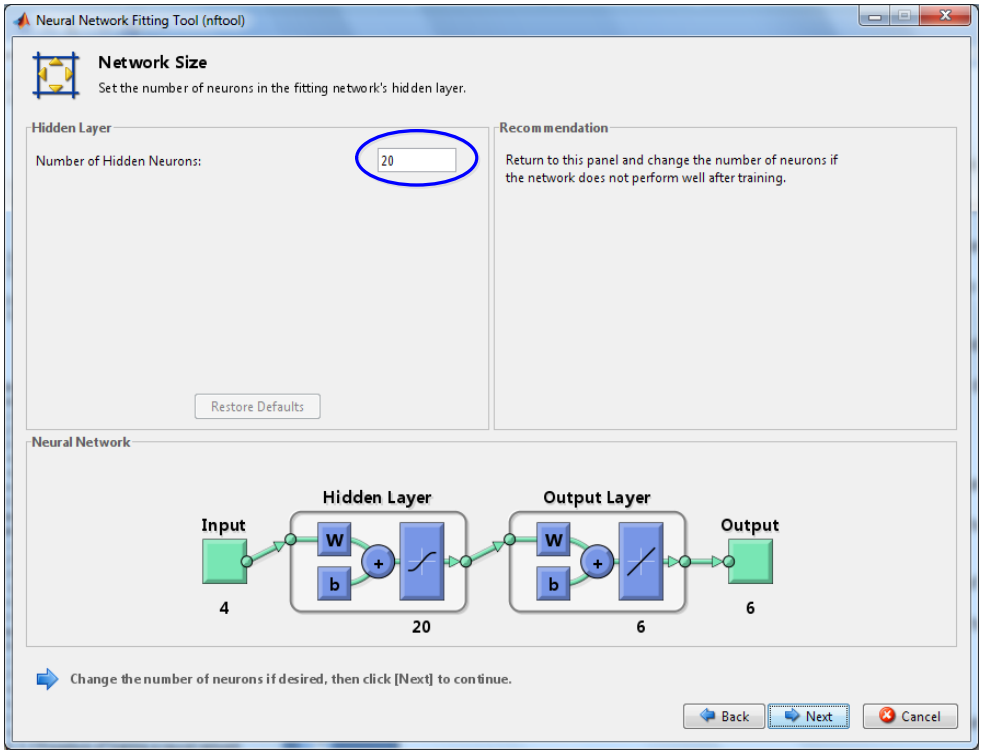

**Appendix A Figure 7-1: The Neural Network Fitting Tool.**



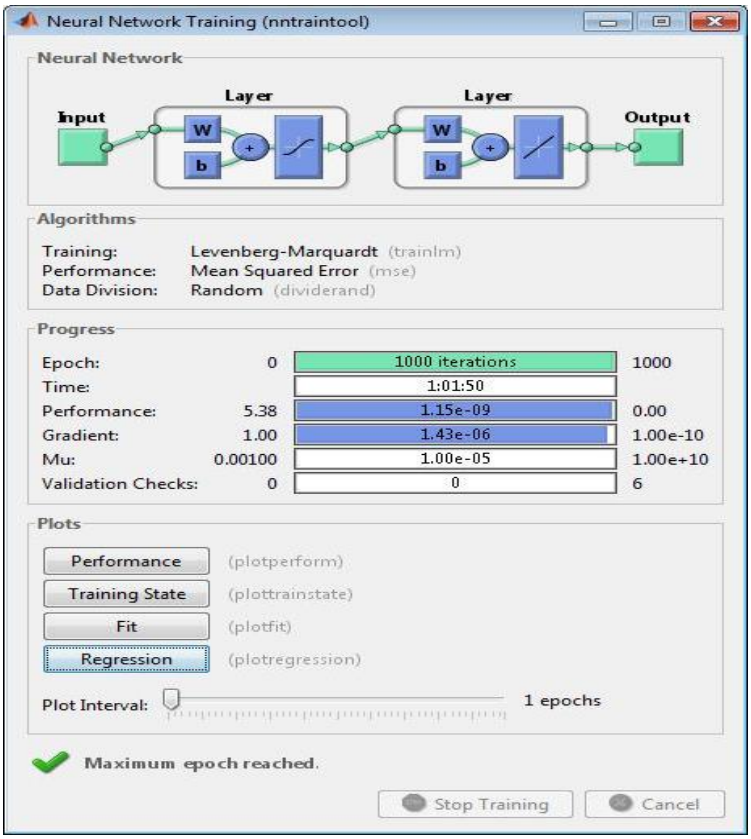

**Appendix A Figure 7-2: Select Input Data as IN and Outputs Data as OUT.**



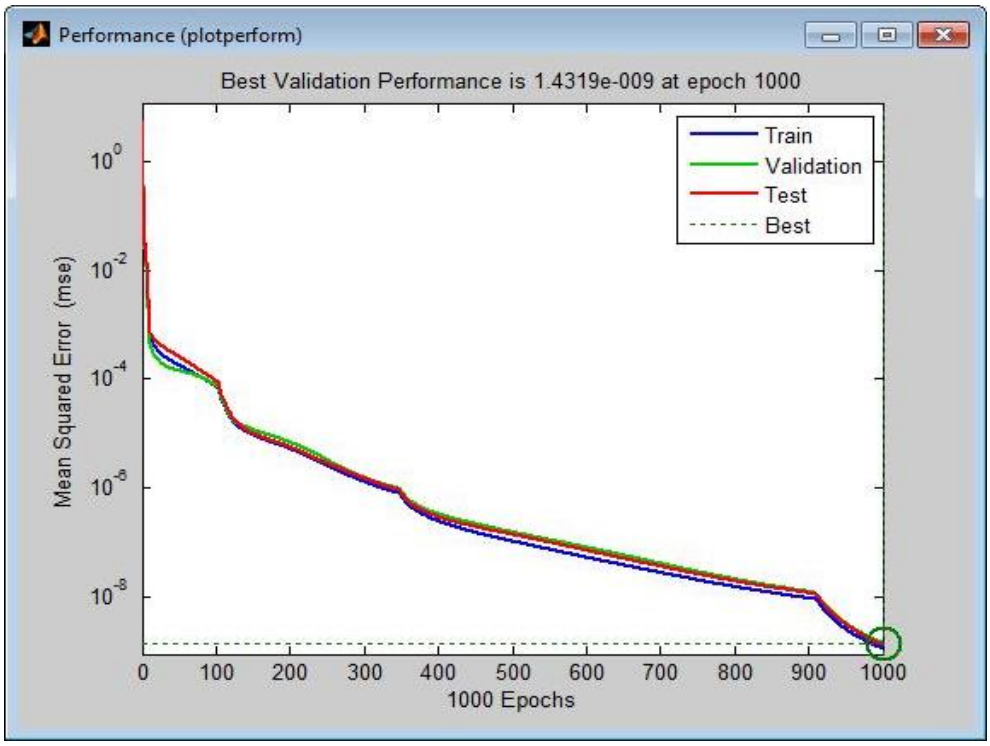

**Appendix A Figure 7-3: The Percentages of Validation and Test Data.**



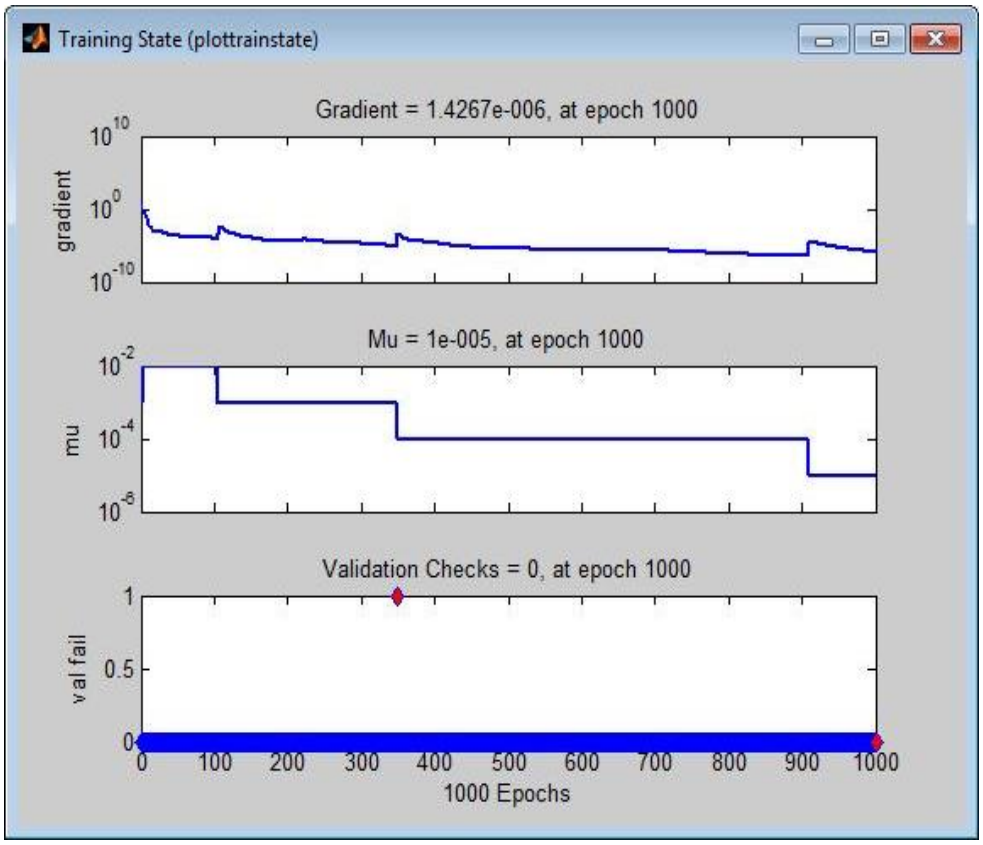

**Appendix A Figure 7-4: Network Size, 20 Hidden Layers.**



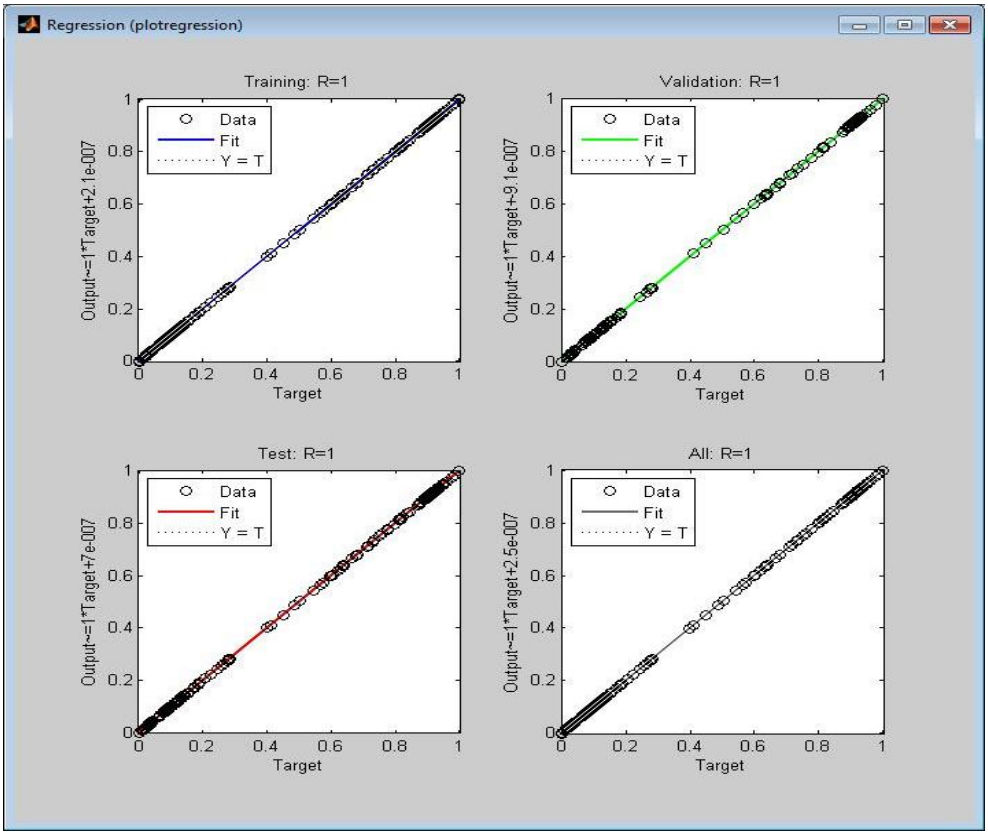

**Appendix A Figure 7-5: Training Results.**



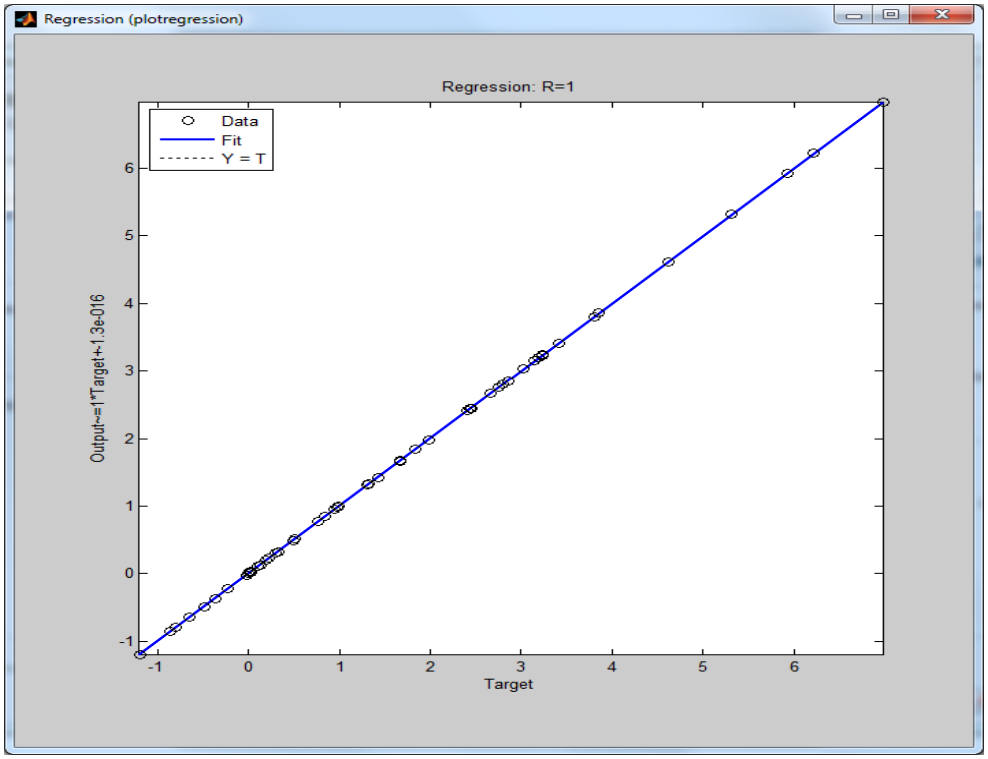

**Appendix A Figure 7-6: The Best Validation Performance Result.**



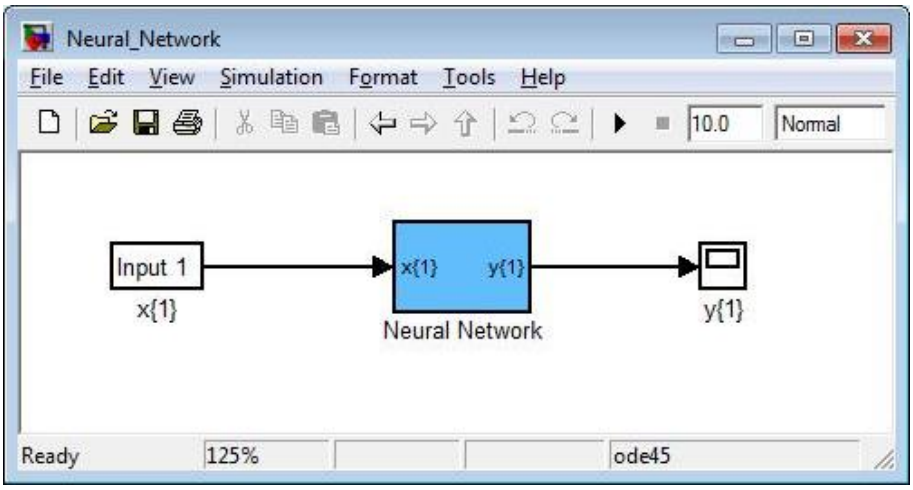

**Appendix A Figure 7-7: Training States.**




**Appendix A Figure 7-8: Training, Validation and Test Result.**

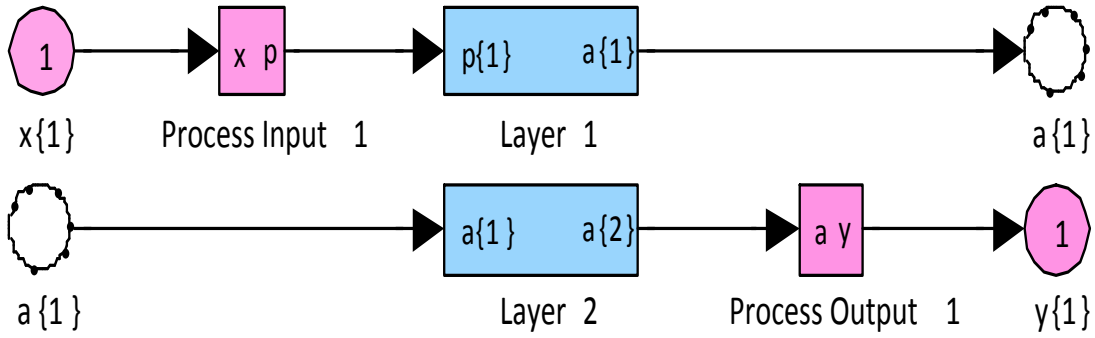



**Appendix A Figure 7-9: Training Regression Result.**

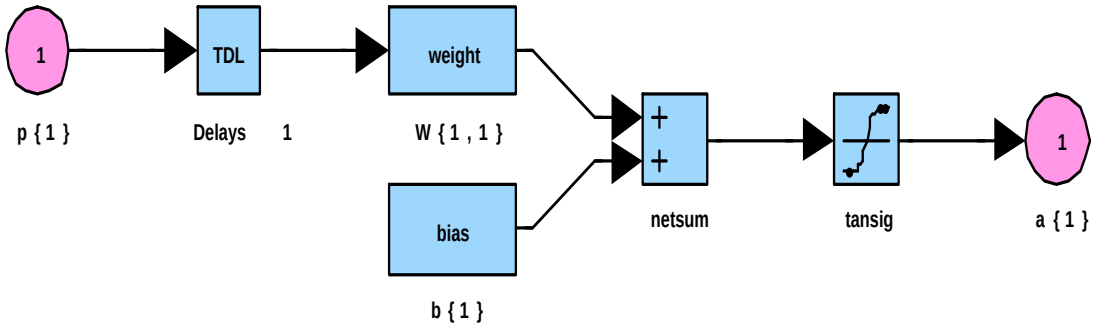



**Appendix A Figure 7-10: Neural Network Simulink Model.**

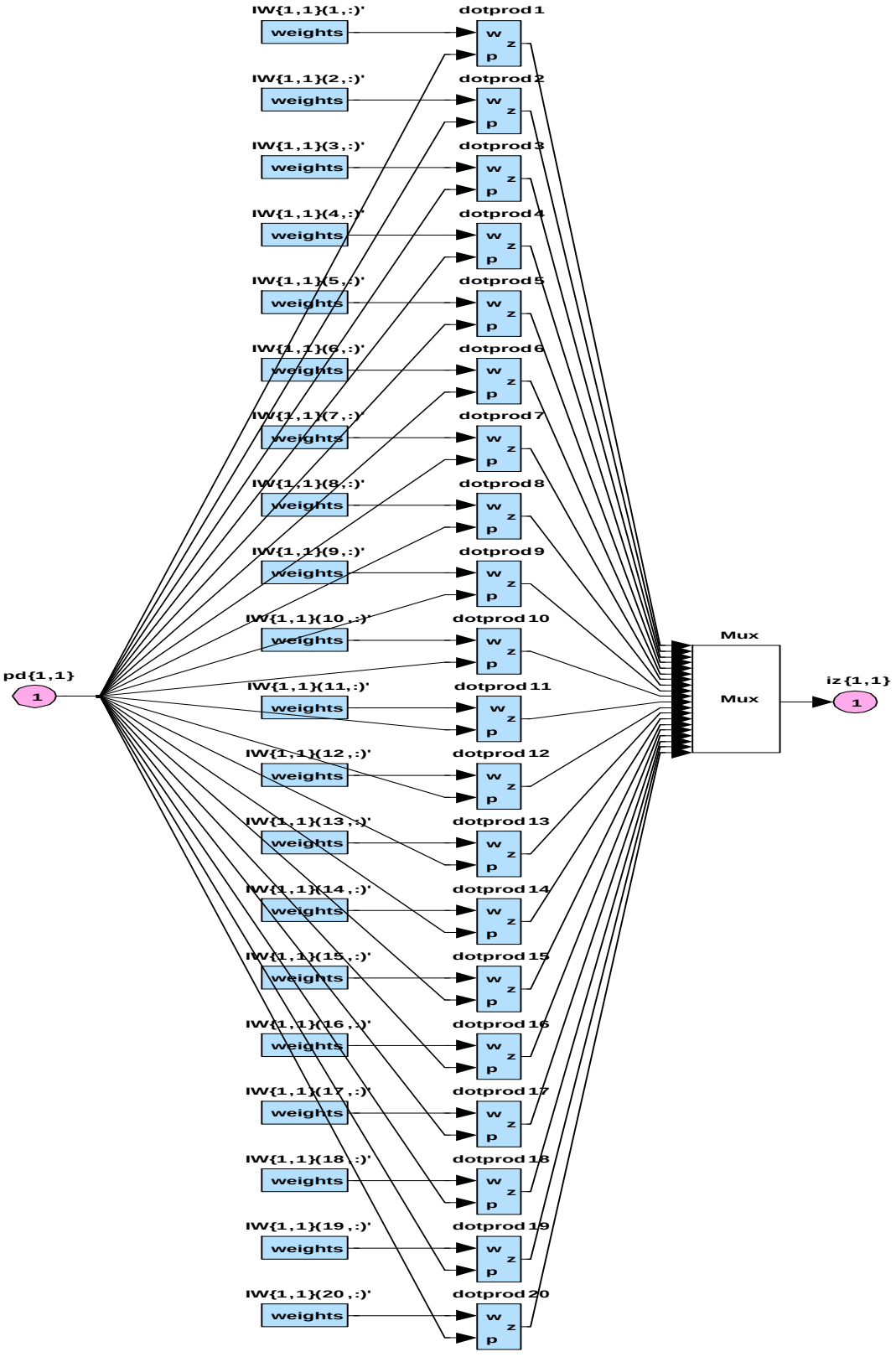
## APPENDIX B: NEURAL NETWORK MODEL



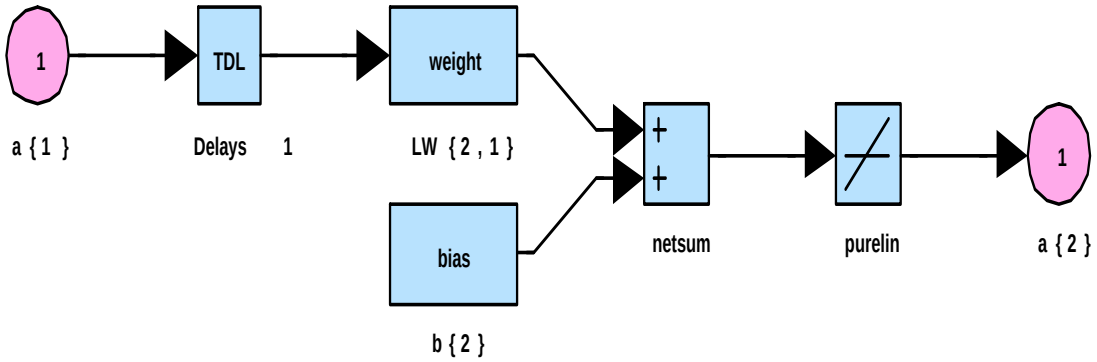

**Appendix B Figure 7-1: Simulink Block Diagram of Neural Network Model.**



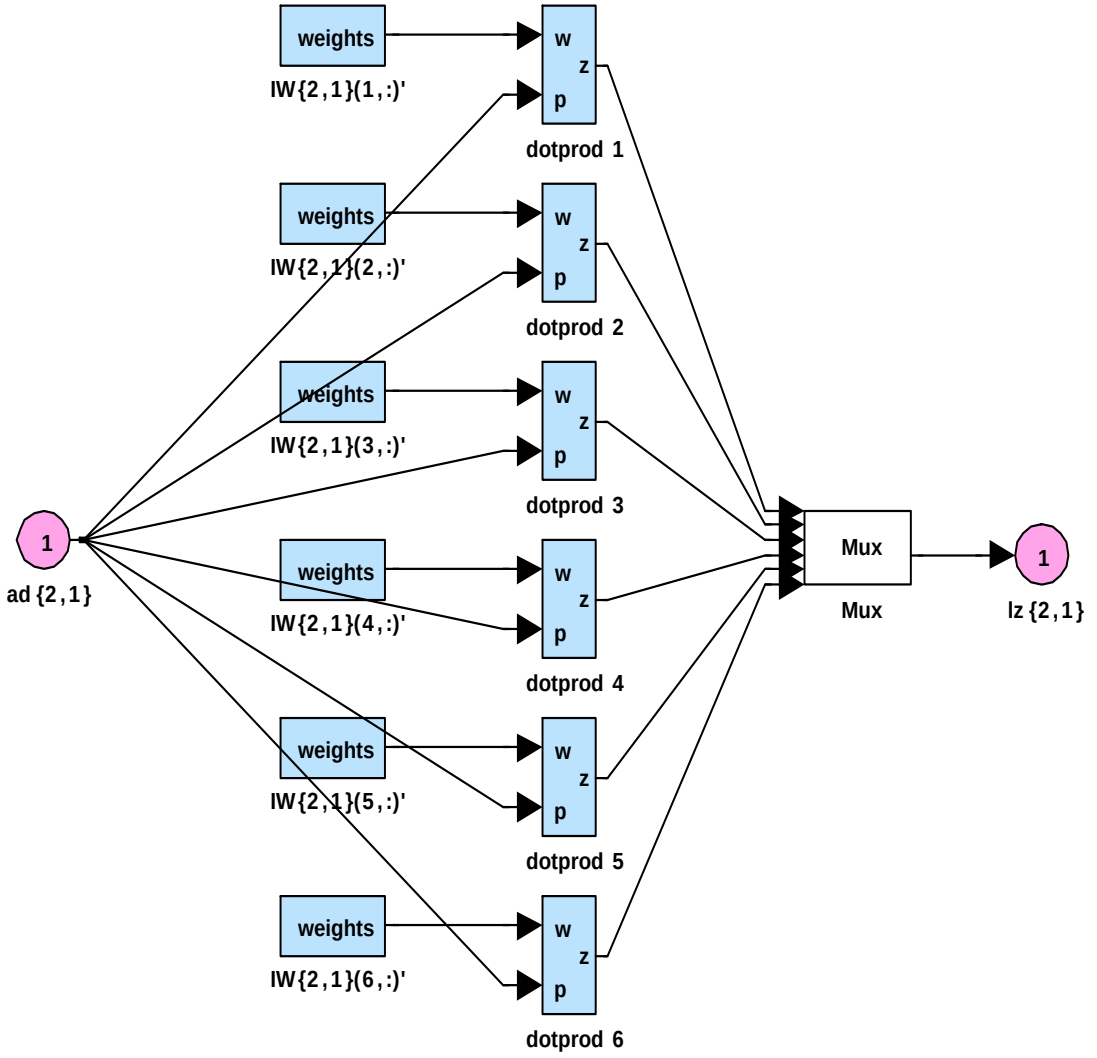

**Appendix B Figure 7-2: Simulink Block Diagram of Hidden Layer (Layer 1).**




**Appendix B Figure 7-3: Simulink Block Diagram of Hidden Layer with 20 Neurons.**




**Appendix B Figure 7-4:** ***Simulink Block Diagram of Output Layer (Layer 2).***




**Appendix B Figure 7-5:** ***Simulink Block Diagram of Output Layer with 6 Neurons.***

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